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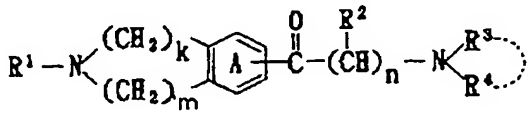
(54) Condensed heterocyclic ketone derivatives, their production and use.

(57) A compound of the formula:



[I]

wherein R^1 is H or an optionally substituted hydrocarbon or acyl group; ring A is an optionally further substituted benzene ring; n is an integer of 1 to 10; R^2, R^3 and R^4 are H or an optionally substituted hydrocarbon group; R^3 and R^4 may form an optionally substituted heterocyclic group, taken together with the adjacent nitrogen atom; k is an integer of 0 to 3; and m is an integer of 1 to 8; provided that when k = 0 and m = 2, n is an integer of not less than 2 or a pharmaceutically acceptable salt thereof, exhibiting excellent cholinesterase inhibitory activity and monoamine reuptake inhibitory activity, thus being useful as therapeutic/prophylactic medicaments of senile dementia.

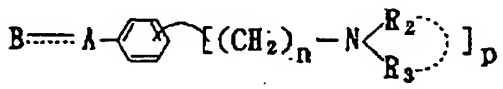
EP 0 560 235 A1

This invention relates to novel condensed heterocyclic ketone derivatives and salts thereof. These compounds are useful as medicines, more specifically, cholinesterase inhibitors, especially as therapeutic or/and prophylactic agents for senile dementia, Alzheimer's disease and so on.

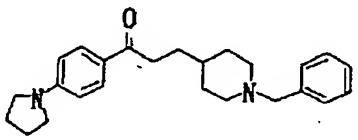
With an increasing number of elderly people, there have been proposed various compounds having therapeutic or/and prophylactic actions on senile dementia. Among them, in physostigmine, a naturally-occurring cholinesterase inhibitor, there has been found therapeutic or/and prophylactic actions on senile dementia (International Journal of Clinical Pharmacology, Therapy and Toxicology, Vol. 29, No. 1, p. 23-37-(1991) etc.). Physostigmine is, however, possessed of such drawbacks as relatively short duration of the action and high toxicity.

On the other hand, various heterocyclic compounds have been proposed as synthetic medicines (for example, in EP-A-0,378,207, USP 4,849,431 and USP 4,895,841, cholinesterase inhibitors having N-containing heterocyclic ring being described, and, in JPA S52(1977)-72829 and JPA S55(1980)-9070, antidepressant or antianxiety drugs having chemical structures analogous to the above-mentioned cholinesterase inhibitor being described).

More specifically, in EP-A-0,378,207, there are disclosed cyclic amine compounds represented by the formula:



wherein B stands for an optionally substituted saturated or unsaturated 5- to 7-membered azaheterocyclic group; A stands for a bond or an alkylene group or alkenylene group optionally substituted with a hydrocarbon residue,oxo group or hydroxyl group; ----- means single bond or double bond (provided that, when A stands for a bond, ----- means single bond); R_2 and R_3 independently stand for H or an optionally substituted hydrocarbon residue (provided that they are not H at the same time) or may form a cyclic amino group taken together with the adjacent nitrogen atom; n denotes 0, 1 or 2; p denotes 1 or 2, or salts thereof, practically the following compound, among others.

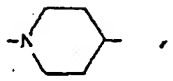


In USP 4,849,431, there are disclosed piperidine derivatives represented by the formula:

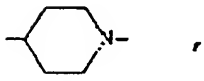
wherein R^1 stands for a monovalent group derived from a member selected from optionally substituted benzene, pyridine, pyrazine, indole, anthraquinone, quinoline, optionally substituted phthalimide, homophthalimide, pyridine carboxylimide, pyridine-N-oxide, pyrazine carboxylimide, naphthalenedicarboxylimide, optionally substituted quinazolinedione, 1,8-naphthalimide, bicyclo[2,2,2]oct-5-ene-2,3-dicarboxylimide and pyromellylimide;

X stands for a group shown by the formula: $-(CH_2)_m-$(wherein m denotes a whole number of 0 to 7), a group shown by the formula: $-O(CH_2)_n-$, a group shown by the formula: $-S(CH_2)_n$, a group shown by the formula: $-NH(CH_2)_n-$, a group shown by the formula: $-SO_2NH(CH_2)_n-$, a group shown by the formula: $-NH-CO-(CH_2)_n-$, a group shown by the formula: $-NH(CH_2)_n-CO-$, a group shown by the formula: $-CO-NR^3-(CH_2)_n-$ (in the definition of X, n in the above formulae denotes a whole number of 1 to 7, and R^3 stands for a lower alkyl or benzyl group), a group shown by the formula: $-O-CH_2CH_2CH(CH_3)-$, a group shown by the formula: $-O-CH_2CH_2CH=$, or a group shown by the formula: $-O-CH_2CH(OH)CH_2-$;

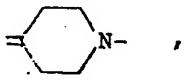
Ring A stands for a group shown by the formula:



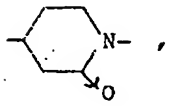
a group shown by the formula:



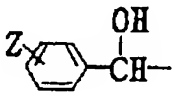
a group shown by the formula:



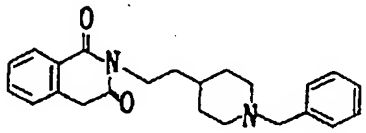
a group shown by the formula:



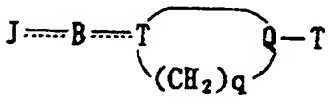
R^2 stands for H, a lower alkyl group, optionally substituted benzyl group, optionally substituted benzoyl group, pyridyl group, 2-hydroxyethyl group, pyridylmethyl group, or a group shown by the formula:



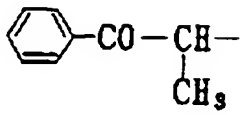
(wherein Z stands for a halogen atom), or pharmaceutically acceptable salts thereof, practically the following compound .



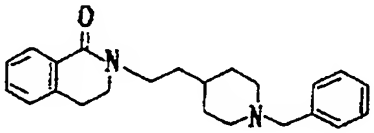
In USP 4,895,841, there are disclosed cyclic amine derivatives represented by the general formula:



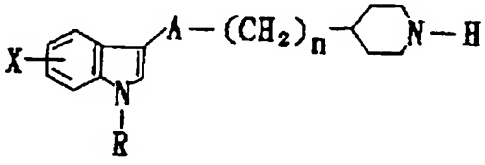
wherein J stands for (a) optionally substituted groups shown as follows; (1) phenyl group, (2) pyridyl group, (3) pyrazyl group, (4) quinolyl group, (5) cyclohexyl group, (6) quinoxalyl group or (7) furyl group,
(b) a mono- or di-valent group selected from the following groups optionally substituted with phenyl group; (1) indanyl, (2) indanonyl, (3) indenyl, (4) indenonyl, (5) indanedionyl, (6) tetralonyl, (7) benzsperonyl, (8) indanolyl, (9) group shown by the formula:



(c) a monovalent group derived from a cyclic amido compound,
(d) a lower alkyl group, or
(e) a group shown by the formula: R^1-CH = CH- (wherein R^1 stands for H or a lower alkoxycarbonyl group);
B stands for a group shown by the formula: -$(C(R^2)H)_n$-,a group shown by the formula: -CO-$(C(R^2)H)_n$-, a group shown by the formula: -NR^2-$(C(R^2)H)_n$- (wherein R^2 stands for H, a lower alkyl group, acyl group, a lower alkylsulfonyl group, optionally substituted phenyl group or benzyl group), a group shown by the formula: - CO-NR^4-$(C(R^2)H)_n$- (wherein R^4 stands for H, a lower alkyl group or phenyl group), a group shown by the formula: -CH = CH-$(C(R^2)H)_n$-, a group shown by the formula: -O-COO-$(C(R^2)H)_n$-, a group shown by the formula: -O-CO-NH-$(C(R^2)H)_n$, a group shown by the formula: -NH-CO-$(C(R^2)H)_n$-, a group shown by the formula: -CH_2-CO-NH-$(C(R^2)H)_n$-, a group shown by the formula: -CO-NH-$(C(R^2)H)_n$-, a group shown by the formula: -C(OH)H-$(C(R^2)H_n$- (in the above formulae, n denotes 0 or a whole number of 1 to 10, R^2 stands for H or methyl group in the form of alkylene group shown by the formula: -$(C(R^2)H)_n$- which is unsubstituted or having one or more than one methyl group), a group shown by the formula: =(CH-CH = CH)$_b$- (wherein b denotes a whole number of 1 to 3), a group shown by the formula: =CH-$(CH_2)_c$- (wherein c denotes a whole number of 1 to 9), a group shown by the formula: =$(CH\text{-}CH)_d$= (wherein d denotes 0 or a whole number of 1 to 5), a group shown by the formula: -CO-CH = CH-CH_2-, a group shown by the formula: -$C(CH_3)$H-CO-NH-CH_2-, a group shown by the formula: -CH = CH-CO-NH-$(CH_2)_2$-, the group shown by the formula: -NH-, the group shown by the formula: -O-, the group shown by the formula: -S-, dialkylaminoalkylcarbonyl group or a lower alkoxycarbonyl group,
T stands for N or C,
Q stands for N, C or a group shown by the formula: >N→ O,
K stands for H, an optionally substituted phenyl group, an arylalkyl group optionally substituted with phenyl group, a cinnamyl group optionally substituted with phenyl group, a lower alkyl group, pyridylmethyl group, cycloalkylalkyl group, adamantanemethyl group, furylmethyl group, cycloalkyl group, a lower alkoxycarbonyl group or acyl group,
q denotes a whole number of 1 to 3, and ----- denotes a single bond or a double bond
or their pharmaceutically acceptable salts, a practical embodiment being the following compound.

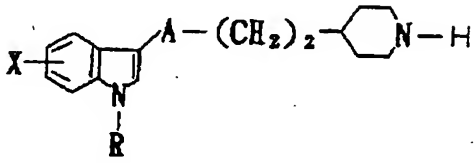


In USP4,064,255, there are disclosed pharmaceutical compositions containing a compound represented by the general formula:



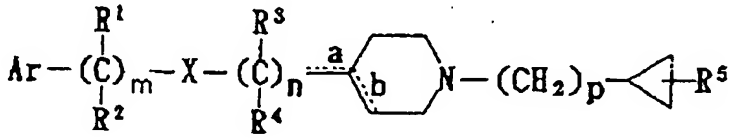
wherein R stands for H, a C_{1-4} alkyl group or an aralkyl group whose alkyl moiety has one or two carbon atoms; X stands for H or a halogen atom, alkyl, alkoxy or alkylthio group, each optionally having one to four carbon atoms, trifluoromethyl, nitro, hydroxyl or unsubstituted amino group or amino group substituted with one or two alkyl groups or acyl or alkylsulfonyl group; A stands for the group -CO- or the group -CH_2-; and n denotes 0, 1 or 2, or a pharmaceutically acceptable salt thereof, which are useful in treatment of pathological conditions caused by disturbances in serotonin systems, and, in USP 4,208,417, there are

disclosed indole derivatives represented by the general formula:



wherein R stands for H, a C_{1-4} alkyl group or an aralkyl group whose alkyl moiety has one or two carbon atoms; X stands for H or a halogen atom, alkyl group, alkoxy group or an alkylthio group whose alkyl moiety has one to four carbon atoms; A stands for -CO- or $-CH_2-$; and n denotes 1 or 2, which are medicinally active compounds having affinity for the ^{3}H-diazepam binding site.

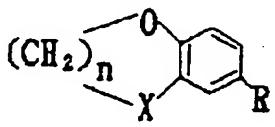
Further, in WO91/03243, there are disclosed compounds represented by the general formula:



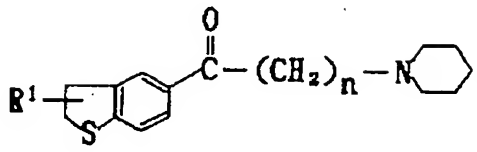
wherein m denotes 0 to 3; n denotes 0 to 3; m and n are not 0 simultaneously; p denotes 0 to 3; X stands for O, S, SO, SO_2, NR^6, CR^7R^8, CO or CHOH; R^1, R^3 and R^7 each stand for H, C_{1-5} alkyl, halogen, $NR^{10}R^{11}$, OH, COOH, C_{2-6} carboalkoxy, CN, Ar, C_{1-5} alkoxy or C_{1-5} alkylthio; R^2, R^4 and R^8 each stand for H, C_{1-5} alkyl, C_{2-6} carboalkoxy, CN, C_{1-5} alkoxy or Ar^1; when X is O, S, SO, SO_2 or NR^6, R^1, R^2, R^3 and R^4 are not C_{1-5} alkoxy, C_{1-5} alkylthio, $NR^{10}R^{11}$ or OH; R^5 stands for H, alkyl, halogen, OH or alkenyl; R^6 stands for H, C_{1-5} alkyl or Ar^1; Ar and Ar^1 respectively stand for naphthyl, pyridyl, pyrimidyl, indolyl, quinolinyl or phenyl, these groups being optionally substituted with C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl having 1 to 7 halogen atoms, SH, $S(O)_t$-C_{1-3} alkyl (t denotes 1, 2 or 3), C_{2-6} dialkylamino, halogen, C_{1-3} alkylamino, NH_2, CN, NO_2, SO_3H, tetrazole, COOH, C_{2-6} carboalcoxy, $CONH_2$, SO_2NO_2, COR^9, $CONR^{12}R^{13}$, $SO_2NR^{12}R^{13}$, Ar^2, OAr^2 or SAr^2; Ar^2 stands for naphthyl group or phenyl group, these groups being optionally substituted with C_{1-3} alkyl, C_{1-3} haloalkyl having one to seven halogen atoms, C_{1-3} alkoxy, halogen or C_{1-3} alkylthio; R^9, R^{10}, R^{11}, R^{12} and R^{13} respectively stand for H, C_{1-5} alkyl or phenyl, R^{10} and R^{11} may, taken together, form C_{3-6} alkylene chain, R^{12} and R^{13} may, taken together, form C_{3-6} alkylene chain; a or b shows double bond or single bond, and both are not double bond; or pharmaceutically acceptable salts thereof, which are useful in the treatment of physiological or drug-induced psychosis or dyskinesia.

On the other hand, a variety of O-containing or S-containing condensed ketone derivatives have been produced, and their biological activity and pharmacological actions are disclosed. However, nothing was disclosed on the actions as cholinesterase inhibitor and therapeutic or/and prophylactic agents of senile dementia.

More specifically, in Chem. Abstr., 107, 190332h (1987), there is disclosed that the compound represented by the general formula:

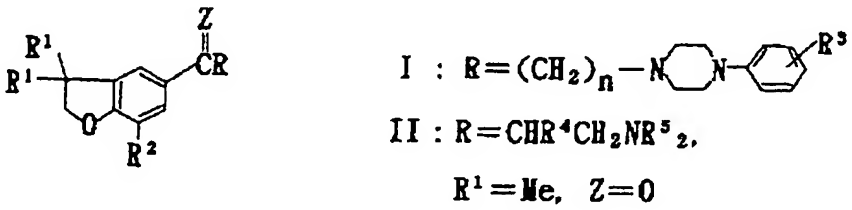


(wherein R = Ac, COEt, COPr, $COCHMe_2$, $CO(CH_2)_2Cl$, $CO(CH_2)_3Cl$, $COCH_2NMe_2$, $CO(CH_2)_2NMe_2$, $CO(CH_2)_3NMe_2$, and salts of them or R = COCH = CHPh, X = CH_2 or O, n = 1, 2 or 3) has an antiinflammatory action. In Chem. Abstr., 89, 36594y (1978), there is disclosed that the compound represented by the general formula:



(wherein R^1 = H, Me; n = 2, 3) has a convulsive action, an arterial blood pressure lowering action and a local anesthetic action.

In Chem. Abstr., 87, 152125d (1977), there is disclosed that the compound represented by the general formula:

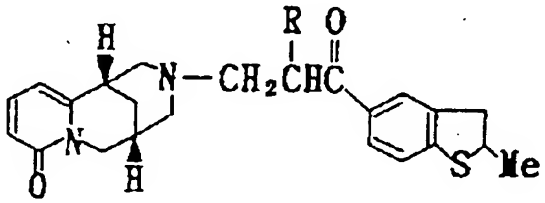


wherein R^1 = H, Me; R^2 = H, Cl, Me; R^3 = H, F, Me, OMe, Cl; n = 1, 2, 3; Z = O, OH, H (for Compound I) or R^2 = H, Cl; R^4 = H, Me; NR^5 = NMe_2, morpholino, piperidino (for Compound II) has an antidepressant action.

In EP-163,537, there is disclosed the compound represented by the general formula:

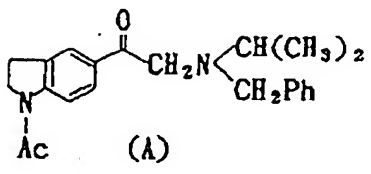
(wherein R = 4-cycloalkylphenyl, 3,4-methylenedioxyphenyl, 2,3-dihydro-5-benzofuranyl; R^1 = alkyl, cycloalkyl, cyclopentylmethyl; R^2 = optionally substituted pyrrolidino, piperidino, hexahydro-1H-azepin-1-yl, octahydro-1-azocinyl) has a muscle-relaxing action.

In Chem.Abstr., 91, 211631y (1979), there is disclosed that the compound represented by the formula:

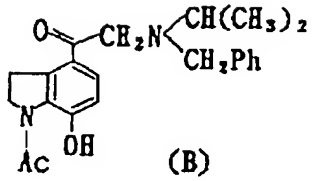


(wherein R = H, Me) is synthesized as a derivative of cytisine, an alkaloid, having an anticholinergic action.

And, as N-containing condensed heterocyclic ketone derivative, in Helvetica Chimica Acta, 51, 1616 (1968), the compounds represented by the formula (A) and the formula (B):

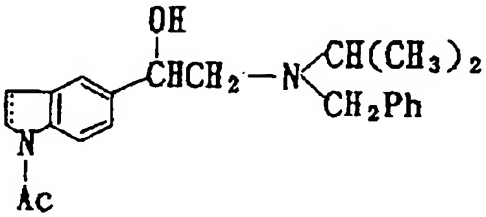


(A)



(B)

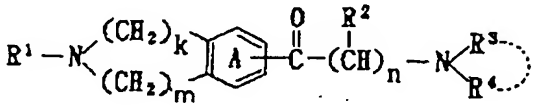
are disclosed as intermediates for synthesizing alkanolamine, an agent of acting on sympathetic nervous system, represented by the formula (C):



In these days when senile dementia is increasing, however, there is needed development of excellent therapeutic or/and prophylactic agents having a stronger action and longer action and less toxicity than the compounds already known to have therapeutic or/and prophylactic efficacy on senile dementia.

The present invention was accomplished by succeeding in creation of novel compounds having a condensed heterocyclic group of specific chemical structure and by finding that these novel compounds have unexpectedly excellent cholinesterase inhibitory activity and monoamine reuptake inhibitory activity, thus being useful as therapeutic or/and prophylactic agents for senile dementia. More specifically, the present invention relates to;

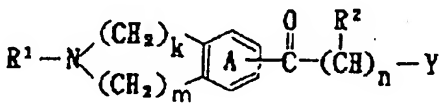
(1) condensed heterocyclic ketone derivatives of the formula:



[I]

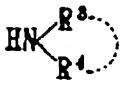
wherein R^1 stands for H, an optionally substituted hydrocarbon group or an optionally substituted acyl group; ring A stands for an optionally further substituted benzene ring; n denotes a whole number of 1 to 10; R^2, R^3 and R^4 independently stand for H or an optionally substituted hydrocarbon group; R^3 and R^4 may form an optionally substituted heterocyclic group, taken together with the adjacent nitrogen atom; R^2's may be different from one another in the repetition of n; k denotes a whole number of 0 to 3; and m denotes a whole number of 1 to 8; provided that when k = 0 and m = 2, n denotes a whole number of not less than 2, or salts thereof,

(2) a method of producing the compound [I] or a salt thereof, which comprises reacting a compound represented by the formula:



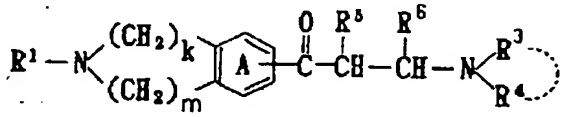
[II]

wherein Y stands for a leaving group; R^1, ring A, R^2, n, k and m are of the same meanings as defined above, or a salt thereof with a compound represented by the formula:



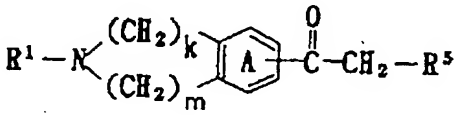
[III]

wherein R^3 and R^4 are of the same meanings as defined above, or a salt thereof,
(3) a method of producing a compound represented by the formula:



[VI]

wherein R^1, R^3, R^4, ring A, k and m are of the same meanings as defined above, R^5 stands for H or an optionally substituted hydrocarbon group, and R^6 stands for H or an optionally substituted hydrocarbon group, or a salt thereof, which comprises reacting a compound represented by the formula:

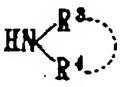


[IV]

wherein R^1, R^5, ring A, k and m are of the same meanings as defined above, or a salt thereof and a compound represented by the formula:

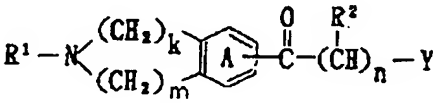
R^6-CHO [V]

wherein R^6 is of the same meaning as defined above with a compound represented by the formula



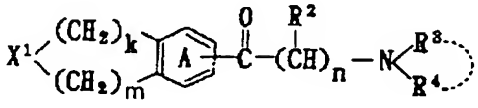
[III]

wherein R^3 and R^4 are of the same meanings as defined above, or a salt thereof,
(4) compounds represented by the formula:



[II]

wherein Y, R^1, ring A, R^2, n, k and m are of the same meanings as defined above, or salts thereof,
(5) a cholinesterase inhibitor, which contains a condensed heterocyclic ketone derivative represented by the formula:



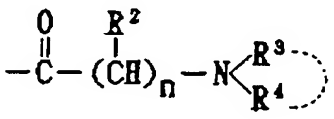
[VII]

wherein X^1 stands for R^1-N (wherein R^1 stands for H, an optionally substituted hydrocarbon group or an optionally substituted acyl group), O or S; ring A stands for an optionally further substituted benzene ring; n denotes a whole number of 1 to 10; R^2, R^3 and R^4 independently stand for H or an optionally

substituted hydrocarbon group; R^3 and R^4 may form an optionally substituted heterocyclic group, taken together with the adjacent nitrogen atom; R^2's may be different from one another in the repetition of n; k denotes a whole number of 0 to 3; and m denotes a whole number of 1 to 8, or a salt thereof, and

(6) a therapeutic or/and prophylactic agent for senile dementia which contains the compound [VII] or a salt thereof.

The compound [I] or salts thereof of this invention are novel compounds having structural characteristics in that the heterocyclic ring containing a hetero atom (O, S or N) condensed on the benzene ring is saturated one and a substituent



is bonded to the carbon atom on the benzene ring, and, based on these characteristics, these compounds show excellent therapeutic or/and prophylactic actions for senile dementia.

In the foregoing formulae, R^1 stands for H, an optionally substituted hydrocarbon group or an optionally substituted acyl group.

R^2 stands for H or an optionally substituted hydrocarbon group, and R^2's may be different from one another in the repetition of n.

R^3 and R^4 stand for H or an optionally substituted hydrocarbon group, and, they may form, taken together with the adjacent nitrogen atom, an optionally substituted heterocyclic group.

R^5 and R^6 stand for H or an optionally substituted hydrocarbon group.

Examples of "hydrocarbon group" of "optionally substituted hydrocarbon group" shown by the above-mentioned R^1, R^2, R^3, R^4, R^5 and R^6 include chain-like or cyclic or their combined type C_{1-18} hydrocarbon groups. Examples of the chain-like hydrocarbon groups include straight-chain or branched C_{1-11} alkyl groups (e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, tert-butyl, n-pentyl, n-hexyl, etc.), straight-chain or branched C_{2-4} alkenyl groups (e.g. vinyl, allyl, 2-butenyl, etc.) and straight-chain or branched C_{2-4} alkynyl groups (e.g. propargyl, 2-butynyl, etc.). Examples of the cyclic hydrocarbon groups include C_{3-7} monocyclic cycloalkyl groups (e.g. cyclobutyl, cyclopentyl, cyclohexyl etc.), C_{8-14} bridge ring saturated hydrocarbon groups (e.g. bicyclo[3.2.1]oct-2-yl, bicyclo[3.3.1]non-2-yl, adamantan-1-yl, etc.), C_{6-14} aryl groups (e.g. phenyl group, naphthyl group, etc.), among others.

Examples of hydrocarbon groups composed of chain-like and cyclic ones include C_{7-18} aralkyl (phenyl-C_{1-12} alkyl or naphthyl-C_{1-8} alkyl such as phenylmethyl, phenylethyl, phenylpropyl, phenylbutyl, phenylpentyl, phenylhexyl or α-naphthylmethyl; diphenyl-C_{1-3} alkyl such as diphenylmethyl or diphenylethyl), C_{6-14} aryl-C_{2-12} alkenyl (phenyl-C_{2-12} alkenyl such as styryl, cinnamyl, 4-phenyl-2-butenyl or 4-phenyl-3-butenyl), C_{6-14} aryl-C_{2-12} alkynyl (phenyl-C_{2-12} alkynyl such as phenylethynyl, 3-phenyl-2-propynyl or 3-phenyl-1-propynyl), C_{3-7} cycloalkyl-C_{1-6} alkyl (e.g. cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, cyclopropylethyl, cyclobutylethyl, cyclopentylethyl, cyclohexylethyl, cycloheptylethyl, cyclopropylpropyl, cyclobutylpropyl, cyclopentylpropyl, cyclohexylpropyl, cycloheptylpropyl, cyclopropylbutyl, cyclobutylbutyl, cyclopentylbutyl, cyclohexylbutyl, cycloheptylbutyl, cyclopropylpentyl, cyclobutylpentyl, cyclopentylpentyl, cyclohexylpentyl, cycloheptylpentyl, cyclopropylhexyl, cyclobutylhexyl, cyclopentylhexyl, cyclohexylhexyl, cycloheptylhexyl, etc.).

Preferable examples of the "hydrocarbon group" of the "optionally substituted hydrocarbon group" shown by R^1, R^2, R^3, R^4, R^5 and R^6 include straight-chain or branched C_{1-11} alkyl groups, especially straight-chain or branched C_{1-7} alkyl groups (e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, tert-butyl, n-pentyl, n-hexyl, etc.) or C_{7-18} aralkyl groups, especially C_{7-10} aralkyl groups (e.g. phenyl-C_{1-4} alkyl such as phenylmethyl, phenylethyl and phenylpropyl).

The hydrocarbon groups shown by R^1, R^2, R^3, R^4, R^5 and R^6 may optionally have substituents, and, as such substituents, use is properly made of those generally used as substituents of hydrocarbon groups. More specifically, as substituents which the above-mentioned C_{1-11} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} monocyclic cycloalkyl and C_{8-14} bridge ring saturated hydrocarbon groups may have, use is made of one to five of those selected from halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro group, cyano group, hydroxyl group, C_{1-4} alkoxy groups (e.g. methoxy, ethoxy, propyloxy, butyloxy, isopropyloxy, etc.), C_{1-4} alkylthio groups (e.g. methylthio, ethylthio, propylthio, etc.), amino group, mono- or di- C_{1-4} alkylamino group (e.g. methylamino, ethylamino, propylamino, dimethylamino, diethylamino, etc.), 5- to 7-membered cyclic amino groups (e.g. pyrrolidino, piperidino, morpholino, etc.), C_{1-4} alkyl-carbonylamino

groups (e.g. acetylamino, propionylamino, butyrylamino, etc.), C_{1-4} alkylsulfonylamino groups (e.g. methylsulfonylamino, ethylsulfonylamino, etc.), C_{1-4} alkoxy-carbonyl groups (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, etc.), carboxyl group, C_{1-6} alkyl-carbonyl groups (e.g. methylcarbonyl, ethylcarbonyl, propylcarbonyl, etc.), carbamoyl group, mono- or di-C_{1-4} alkylcarbamoyl groups (e.g. methylcarbamoyl, ethylcarbamoyl, etc.), C_{1-6} alkylsulfonyl groups (e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl, etc.), C_{1-4} alkylenedioxy (e.g. methylenedioxy, etc.), 5- or 6- membered heterocyclic groups or its condensed ring containing 1 to 3 hetero atoms selected from N,S and O other than carbon atoms which may be substituted with a C_{1-4} alkyl (e.g. pyridyl, pyridinyl, pyrazinyl, pyrimidinyl, quinolinyl, isoquinolinyl, naphthylidinyl, thiazolyl, benzothiazolyl, benzoxazolyl, furyl, furanyl, thiophenyl, etc.).

Examples of the substituents, which the C_{6-14} aryl groups shown by R^1, R^2, R^3, R^4, R^5 and R^6 may have, include C_{1-4} alkyl groups (e.g. methyl, ethyl, propyl, butyl, etc.), halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro group, cyano group, hydroxyl group, C_{1-4} alkoxy groups (e.g. methoxy, ethoxy, propyloxy, butyloxy, isopropyloxy, etc.), C_{1-4} alkylthio groups (e.g. methylthio, ethylthio, propylthio, isopropylthio, butylthio, etc.), amino group, mono- or di-C_{1-4} alkylamino groups (e.g. methylamino, ethylamino, propylamino, dimethylamino, diethylamino, etc.), 5- to 7-membered cyclic amino groups (e.g. pyrrolidino, piperidino, morpholino, etc.), C_{1-4} alkyl-carbonylamino groups (e.g. acetylamino, propionylamino, butyrylamino, etc.), C_{7-18} aralkyloxy (e.g. phenylmethoxy, phenylethoxy, etc.), aminocarbonyloxy group, mono- or di-C_{1-4} alkylaminocarbonyloxy groups (e.g. methylaminocarbonyloxy, ethylaminocarbonyloxy, dimethylaminocarbonyloxy, diethylaminocarbonyloxy, etc.), C_{1-4} alkylsulfonylamino groups (e.g. methylsulfonylamino, ethylsulfonylamino, propylsulfonylamino, etc.), C_{1-4} alkoxy-carbonyl groups (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isobutoxycarbonyl, etc.), carboxyl group, C_{1-6} alkylcarbonyl groups (e.g. methylcarbonyl, ethylcarbonyl, butylcarbonyl, etc.), C_{3-7} cycloalkyl-carbonyl (e.g. cyclohexylcarbonyl, etc.), carbamoyl group, mono- or di-C_{1-4} alkyl-carbamoyl groups (e.g. methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, butylcarbamoyl, diethylcarbamoyl, dibutylcarbamoyl, etc.), C_{1-6} alkylsulfonyl groups (e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl, etc.), C_{3-7} cycloalkylsulfonyl (e.g. cyclopentylsulfonyl, cyclohexylsulfonyl, etc.), C_{1-4} alkylenedioxy (e.g. methylenedioxy, etc.) as well as phenyl, naphthyl, mono- or di-phenyl-C_{1-3} alkyl (e.g. benzyl, diphenylmethyl, etc.), phenoxy, benzoyl, phenoxycarbonyl, benzylcarbonyl, phenyl-C_{1-4} alkylcarbamoyl, phenylcarbamoyl, phenyl-C_{1-4} alkylcarbonylamino, benzoylamino, phenyl-C_{1-4} alkylsulfonyl, phenylsulfonyl, phenyl-C_{1-4} alkylsulfinyl, phenyl-C_{1-4} alkylsulfonylamino or phenylsulfonylamino which may have 1 to 4 substituents selected from the group consisting of C_{1-4} alkyl groups such as methyl, ethyl, propyl, butyl, isopropyl, etc., C_{1-4} alkoxy groups such as methoxy, ethoxy, n-propyloxy, i-propyloxy, n-butyloxy, etc., halogen atoms such as chlorine, bromine, iodine, etc., hydroxyl group, benzyloxy group, amino group, mono- or di-C_{1-4} alkylamino groups as described above, nitro group, C_{1-6} alkyl-carbonyl groups as described above, benzoyl group, etc. The number of substituents which may optionally be substituted on these C_{6-14} aryl groups is suitably about 1 to 5.

As the substituents, which C_{7-18} aralkyl, C_{6-14} aryl-C_{2-12} alkenyl, C_{6-14} aryl-C_{2-12} alkynyl, C_{3-7} cycloalkyl-C_{1-6} alkyl groups may optionally have, use is made of, for example, those similar to the substituents which the above-mentioned C_{6-14} aryl groups may optionally have. Suitable number of the substituents, which these C_{7-18} aralkyl, C_{6-14} aryl-C_{2-12} alkenyl, C_{6-14} aryl-C_{2-12} alkynyl, C_{3-7} cycloalkyl-C_{1-6} alkyl may optionally have, ranges from 1 to 5.

And, R^3 and R^4 may form an optionally substituted heterocyclic group, taken together, with the adjacent nitrogen atom. As the "heterocyclic group" of this "optionally substituted heterocyclic group", use is made of, for example, such heterocyclic groups as containing, other than carbon atoms and one nitrogen atom, optionally 1 to 3 hetero atoms e.g. nitrogen, oxygen or sulfur atom, especially 3- to 13-membered heterocyclic groups. Practically, saturated monocyclic, non-conjugated unsaturated monocyclic, unsaturated monocyclic, polycyclic and bridged heterocyclic groups, for example, are employed.

Examples of the saturated monocyclic heterocyclic group include 5- to 9-membered saturated monocyclic heterocyclic groups such as pyrrolidinyl, piperidinyl, hexamethyleniminyl, heptamethyleniminyl, oxazolidinyl, morpholinyl, thiazolidinyl, thiomorpholinyl, imidazolidinyl, piperazinyl and homopiperazinyl.

Examples of the non-conjugated unsaturated monocyclic or unsaturated monocyclic heterocyclic groups include 5- to 9-membered ones such as pyrrolyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 2-oxazolidonyl, 2-thiazolidonyl, imidazolyl, pyrazolyl and 1,4,5,6-tetrahydropyrimidinyl.

Examples of the polycyclic heterocyclic group include 2,3-dihydro-1H-indolyl, 1,2,3,4-tetrahydroquinolinyl, 2,3,4,5-tetrahydro-1H-1-benzazepinyl, 2,3-dihydro-1H-isoindolyl, 1,2,3,4-tetrahydroisoquinolinyl, 2,3,4,5-tetrahydro-1H-2-benzazepinyl, 2,3,4,5-tetrahydro-1H-3-benzazepinyl, 1,2,3,4,5,6-hexahydro-1-benzazocinyl, 1,2,3,4,5,6-hexahydro-2-benzazocinyl, 1,2,3,4,5,6-hexahydro-3-benzazocinyl, 2,3,4,5,6,7-hexahydro-1H-1-benzazonyl, 2,3,4,5,6,7-hexahydro-1H-2-benzazonyl, 2,3,4,5,6,7-

hexahydro-1H-3-benzazonyl, 2,3,4,5,6,7-hexahydro-1H-4-benzazonyl, β-carbolinyl, phenoxazinyl, phenothiazinyl, indolyl, 3H-3-benzazepinyl, 3,4-dihydroquinolinyl, benzimidalyl, 1,4-benzodiazepinyl, etc.

Examples of the bridged heterocyclic group include 1,8-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]-decanyl, 1,3,8-triazaspiro[4.5]decanyl, 1,5,9-triazaspiro[5.5]undecanyl, 1-oxa-3,9-diazaspiro[5.5]undecanyl, 7-azabicyclo[2.2.1]heptanyl, 8-azabicyclo[3.2.1]octanyl, 9-azabicyclo[3.3.1]nonanyl, etc.

Preferable examples of "heterocyclic group" of "optionally substituted heterocyclic group" optionally formed by R^3 and R^4, taken together, with the adjacent nitrogen atom include the afore-described saturated monocyclic heterocyclic groups, polycyclic heterocyclic groups or bridged heterocyclic groups. Specifically, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 2,3,4,5-tetrahydro-1H-1-benzazepinyl, 2,3,4,5-tetrahydro-1H-2-benzazepinyl, 2,3,4,5-tetrahydro-1H-3-benzazepinyl and 1,3,8-triazaspiro[4,5]decanyl are preferable, especially, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and 1,2,3,4-tetrahydroquinolinyl are often employed.

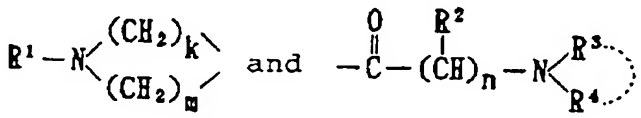
As "substituent" of "optionally substituted heterocyclic group", which may optionally be formed by the above-mentioned R^3 and R^4, taken together, with the adjacent nitrogen atom, use is made of 1 to 5 groups, preferably 1 or 2 groups, selected from, for example, optionally substituted hydrocarbon groups referring to the above-mentioned R^1, R^2, R^3, R^4, R^5 and R^6, halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro group, cyano group, hydroxyl group, C_{1-4} alkoxy groups (e.g. methoxy, ethoxy, propyloxy, butyloxy, isopropyloxy, etc.), C_{1-4} alkylthio groups (e.g. methylthio, ethylthio, propylthio, isopropylthio, etc.), aminogroup, mono- or di-C_{1-4} alkylamino groups (e.g. methyl amino, ethylamino, propylamino, dimethylamino, diethylamino, etc.), C_{1-4} alkylcarbonylamino groups (e.g. acetylamino, propionylamino, butyrylamino, etc.), C_{1-4} alkyl-sulfonylamino groups (e.g. methylsulfonylamino, ethylsulfonylamino, etc.), C_{1-4} alkoxy-carbonyl groups (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, etc.), carboxyl group, formyl group, C_{1-6} alkyl-carbonyl groups (e.g. methylcarbonyl, ethylcarbonyl, propylcarbonyl, etc.), C_{1-4} alkyl-carbonyloxy groups (e.g. acetyloxy, ethylcarbonyloxy, etc.), ω-oxo-ω-(tetrahydrobenzazepinyl)-C_{1-6} alkyl groups (e.g. 1-oxo-1-(tetrahydrobenzazepinyl)methyl, 2-oxo-2-(tetrahydrobenzazepinyl)ethyl, 3-oxo-3-(tetrahydrobenzazepinyl)propyl, etc.), optionally substituted benzoyl groups (herein, as substituents, use is made of 1 to 3 substituents selected from C_{1-4} alkyl, for example, methyl, ethyl, etc., halogen, for example, fluorine, chlorine, bromine, etc., C_{1-4} alkoxy, for example, methoxy, ethoxy, etc., mono- or di-C_{1-4} alkylamino, for example, methylamino, dimethylamino, etc., 5- to 7-membered cyclic amino groups, for example, piperidino, morpholino, etc., nitro, hydroxy, etc.; practical examples of them being benzoyl, 4-fluorobenzoyl, 3,4-dimethoxybenzoyl, etc.), carbamoyl group, mono- or di-C_{1-4} alkylcarbamoyl groups (e.g. methylcarbamoyl, ethylcarbamoyl, etc.), C_{1-6} alkylsulfonyl groups (e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl, etc.), oxo group, the above-mentioned "heterocyclic group" and saturated heterocyclic groups (e.g. pyridyl, pyridinyl, pyrazinyl, pyrimidinyl, quinolinyl, isoquinolinyl, napthylidinyl, benzothiazolyl, benzoxazolyl, furanyl, thiophenyl, etc.). Among them, formyl, C_{1-4} alkylcarbonyloxy groups (e.g. acetyloxy, etc.), hydroxyl group, oxo group, pyridinyl group, optionally substituted benzoyl groups (e.g. benzoyl groups optionally substituted with halogen such as fluorine, chlorine, bromine, etc.), ω-oxo-ω-(tetrahydrobenzazepinyl) C_{1-6} alkyl groups (e.g. 1-oxo-1-(tetrahydrobenzazepinyl)methyl, 2-oxo-2-(tetrahydrobenzazepinyl)ethyl, 3-oxo-3-(tetrahydrobenzazepinyl)propyl, etc.), and optionally substituted hydrocarbon groups referring to the above-mentioned R^1, R^2, R^3, R^4, R^5, and R^6 are preferable. Herein, as optionally substituted hydrocarbon groups referred to in R^1, R^2, R^3, R^4, R^5 and R^6, use is often made of, for example, or straight-chain or branched C_{1-11} alkyl groups, especially straight-chain or branched C_{1-7} alkyl groups (e.g. methyl, ethyl, n-pentyl, n-hexyl, etc.) or C_{7-18} aralkyl groups (e.g. phenyl-C_{1-12} alkyl such as phenylmethyl, phenylethyl, phenylpropyl, phenylhexyl, etc., naphtyl-C_{1-8} alkyl such as α-naphthylmethyl, etc., diphenyl-C_{1-8} alkyl such as diphenylmethyl, etc.), especially C_{7-10} aralkyl groups (e.g. phenylmethyl, phenylethyl, phenylpropyl, etc.), these alkyl and aralkyl groups having optionally halogen (e.g. fluoro, chloro, bromo, etc.), hydroxyl group, C_{1-4} alkylenadioxy (e.g. methylenedioxy, etc.).

As "acyl group" of "optionally substituted acyl group" shown by R^1, use is made of, for example, carboxylic acid acyl groups (e.g. formyl, C_{1-8} alkylcarbonyl or C_{6-14} aryl-carbonyl such as acetyl, propionyl, butyryl, benzoyl, etc.), sulfonic acid acyl groups (e.g. C_{1-7} alkylsulfonyl or C_{6-14} arylsulfonyl such as methanesulfonyl, ethanesulfonyl, propanesulfonyl, benzenesulfonyl, p-toluenesulfonyl, etc.), phosphonic acid acyl groups (e.g. C_{1-7} alkylphosphonyl or C_{6-14} arylphosphonyl such as methanephosphonyl, ethanephosphonyl, propanephosphonyl, benzenephosphonyl, etc,), substituted oxycarbonyl groups (e.g. C_{1-8} alkoxy-carbonyl or C_{7-18} aralkyloxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl, etc.), heterocyclic-carbonyl groups wherein the heterocyclic group is a 5-or 6- membered one containing 1 to 3 hetero atoms selected from N,S and O other than carbon atoms (e.g. pyridylcarbonyl, pyrrolylcarbonyl, quinolylcarbonyl, etc.), carbamoyl group, mono- or di-C_{1-4} alkylcarbamoyl groups (e.g. methylcarbamoyl, ethylcarbamoyl, etc.), etc. Among them, C_{1-8} alkyl-

carbonyl or C_{1-8} alkoxycarbonyl mentioned above is preferable.

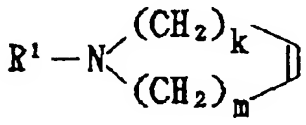
As the substituent which these acyl groups may have, use is made of 1 to 3, preferably 1 to 2 substituents selected from halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.), amino group, mono- or di-C_{1-6} alkylamino groups (e.g. methylamino, ethylamino, propylamino, hexylamino, dimethylamino, diethylamino, etc.) and C_{1-4} alkoxy groups (e.g. methoxy, ethoxy, propoxy, etc.).

The benzene ring shown by ring A may have, besides the groups represented by the formulae



further substituents, and as such substituents, use is made of, for example, those mentioned in reference to C_{6-14} aryl groups of the above-mentioned R^1, R^2, R^3, R^4, R^5 and R^6, the number of them being 1 to 3. Preferable examples of the substituents, which such benzene ring may optionally have, include, among others, halogen such as fluoro, chloro, etc., halogeno-C_{1-3} alkyl such as trifluoromethyl, etc., C_{1-3} alkyl such as methyl, etc. and C_{1-3} alkoxy such as methoxy, etc. Especially, fluoro, for example, is preferable.

The symbol n denotes a whole number of 1 to 10, provided that, in the case of k = 0 and m = 2, n is more than 1. Preferably, n ranges from 2 to 10, especially from 2 to 8. The symbol k denotes a whole number of 0 to 3, and m denotes a whole number of 1 to 8. In other words, the ring



can form a 4- to 14-membered ring.

X^1 stands for R^1-N< (R^1 is of the same meaning as defined above), oxygen atom or sulfur atom.

Preferable examples of R^1 include H, straight-chain or branched C_{1-11} hydrocarbon groups which may be substituted with the above-mentioned substituents (e.g. straight-chain or branched C_{1-11} alkyl such as methyl, ethyl, n-propyl, i-propyl, i-butyl, n-butyl etc., straight-chain or branched C_{2-4} alkenyl such as vinyl, allyl, 2-butenyl etc., straight-chain or branched C_{2-4} alkynyl such as propargyl, 2-butynyl etc.), C_{7-18} aralkyl groups which may be substituted with the above-mentioned substituents (e.g. phenylmethyl, (4-methoxyphenyl) methyl, phenylethyl, phenylpropyl, α-naphthylmethyl etc.), formyl group, C_{1-8} alkyl-carbonyl (e.g. acetyl, propionyl, butyryl etc.), C_{6-14} arylcarbonyl (e.g. benzoyl etc.), C_{1-8} alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl etc.), heterocyclic-carbonyl (e.g. pyridylcarbonyl etc.), carbamoyl, mono- or di-C_{1-4} alkyl-carbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl etc.), etc.; especially H, straight-chain or branched C_{1-4} alkyl groups (e.g. methyl, ethyl, n-propyl, i-propyl, i-butyl, n-butyl etc.), phenyl-C_{1-3} alkyl groups which may be substituted with 1 to 3 substituents selected from C_{1-4} alkyl, halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy and C_{7-18} aralkyloxy (e.g. phenylmethyloxy, (4-methoxyphenyl)methyloxy, phenylethyloxy, phenylpropyloxy etc.), naphthyl-C_{1-3} alkyl (e.g. α-naphtylmethyl, etc.), C_{1-4} alkyl-carbonyl (e.g. acetyl, propionyl, butyryl, etc.), phenyloxycarbonyl, C_{1-4} alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl etc.), etc. More preferable examples of R^1 include H, C_{1-4} alkyl (e.g. methyl, ethyl, propyl, i-propyl, i-butyl, etc.), C_{1-4} alkyl-carbonyl (e.g. acetyl, etc.), phenyl-C_{1-3} alkyl which may be substituted with a C_{1-4} alkoxy (e.g. phenylmethyl, (4-methoxyphenyl)methyl, phenylethyl, etc.); more especially, C_{1-4} alkyl group such as i-butyl, etc. or phenyl-C_{1-3} alkyl which may be substituted by a C_{1-4} alkoxy such as methoxy, etc (e.g. phenylmethyl, (4-methoxyphenyl)methyl, phenylethyl).

As R^2, R^5 and R^6, are preferable H, straight-chain or branched C_{1-3} alkyl groups (e.g. methyl, ethyl, n-propyl, i-propyl), phenyl, etc.; especially H is often the case.

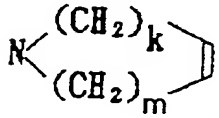
Referring to R^3 and R^4, it is preferable that one of them stands for H or straight-chain or branched C_{1-4} alkyl groups (e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl) and the other stands for straight-chain or branched C_{1-4} alkyl groups, phenyl-C_{1-3} alkyl groups (e.g. phenylmethyl, phenylethyl, phenylpropyl) or naphthyl-C_{1-3} alkyl groups (e.g. α-naphthylmethyl). And, as each of R^3 and R^4, are also preferable straight-chain or branched C_{1-4} alkyl group which may be substituted with a hydroxy (e.g. methyl, ethyl, 2-hydroxyethyl; etc.) or phenyl-C_{1-3} alkyl group which may be substituted with 1 to 3 halogen atoms such as

fluorine, chlorine, bromine, etc. (e.g. phenylmethyl, phenylethyl, 2-chloro-phenylmethyl, etc.).

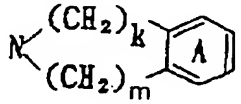
And, such cases as forming heterocyclic rings by R^3 and R^4, taken together, with the adjacent nitrogen atom, are also preferable. Preferable examples include optionally substituted pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 2,3,4,5-tetrahydro-1H-1-benzazepinyl, 2,3,4,5-tetrahydro-1H-2-benzazepinyl, 2,3,4,5-tetrahydro-1H-3-benzazepinyl, 1,3,8-triazaspiro-[4.5]decanyl, etc. especially, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, etc. Especially preferable examples of the substituents on the heterocyclic groups include formyl group, C_{1-4} alkyl-carbonyl groups (e.g. acetyl, etc.), hydroxyl group, oxo group, pyridyl group, an optionally substituted benzoyl group (e.g. benzoyl group which may be substituted with 1 to 3 halogen atoms such as fluorine, chlorine, bromine, etc.), optionally substituted straight-chain or branched C_{1-7} alkyl groups (e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl, tert-butyl, n-pentyl, n-hexyl, which may be substituted with 1 to 3 substituents such as hydroxy group, 5- or 6-membered heterocyclic group containing 1 to 3 hetero atoms of N,S or/and O other than carbon atoms such as pyridyl, furyl, thiazol-4-yl, 2-methyl-thiazol-4-yl, etc.), an optionally substituted phenyl group (e.g. phenyl group which may be substituted with 1 to 3 substituents such as halogen (e.g. fluorine, chlorine, bromine, etc.), hydroxy group, C_{1-4} alkylene-dioxy (e.g. methylenedioxy, etc.), etc.), optionally substituted C_{7-18} aralkyl groups (e.g. phenyl-C_{1-12} alkyl such as phenylmethyl, phenylethyl, phenylpropyl, phenylhexyl, etc., α-naphthylmethyl, diphenyl-C_{1-8} alkyl such as diphenylmethyl, etc., which may be substituted with 1 to 3 substituents such as halogen (e.g. fluorine, chlorine, bromine, etc.), hydroxy group, C_{1-4} alkylenedioxy (e.g. methylenedioxy, etc.), etc.), ω-oxo-ω-(tetrahydrobenzazepinyl)C_{1-6} alkyl (e.g. 1-oxo-1-(tetrahydrobenzazepinyl) methyl, 2-oxo-2-(tetrahdyrobenzazepinyl) ethyl, 3-oxo-3-(tetrahydrobenzazepinyl) propyl, etc.), the number of them being 1 or 2, preferably 1. As R^3 and R^4, most preferable examples are such cases as forming 4-(phenylmethyl)-piperazin-1-ylor 4-[(2-methylthiazol-4-yl)methyl]-piperazin-1-yl, taken together with the adjacent nitrogen atom.

Preferable benzene ring shown by ring A is unsubstituted one.

Referring to k and m, the case where k + m denotes a whole number of 2 to 6 is preferable, namely the case where the moiety

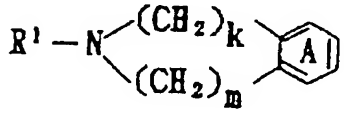


forms a 5- to 9-membered ring. Further, referring to the combination of k and m, it is preferable that, when k is 0, m is 2, 3, 4 or 5; when k is 1, m is 1, 2 or 3; and when k is 2, m is 2. More specifically, preferable examples of N-containing condensed heterocyclic ring represented by the formula:

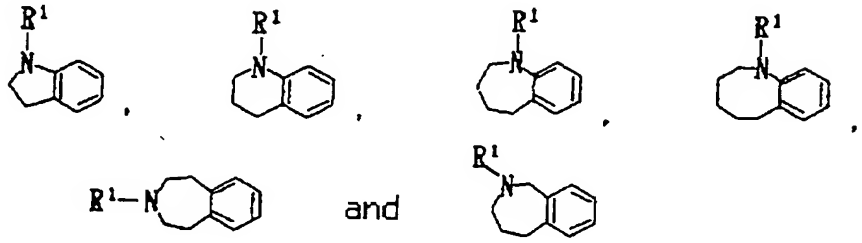


include 2,3-dihydro-1H-indole, 1,2,3,4-tetrahydroquinoline, 2,3,4,5-tetrahydro-1H-1-benzazepine, 2,3-dihydro-1H-isoindole, 1,2,3,4-tetrahydroisoquinoline, 2,3,4,5-tetrahydro-1H-2-benzazepine, 2,3,4,5-tetrahydro-1H-3-benzazepine, 1,2,3,4,5,6-hexahydro-1-benzazocine, 1,2,3,4,5,6-hexahydro-2-benzazocine,1,2,3,4,5,6-hexahydro-3-benzazocine, 2,3,4,5,6,7-hexahydro-1H-1-benzazonine, 2,3,4,5,6,7-hexahydro-1H-2-benzazonine, 2,3,4,5,6,7-hexahydro-1H-3-benzazonine, 2,3,4,5,6,7-hexahydro-1H-4-benzazonine, etc., especially, 2,3,4,5-tetrahydro-1H-3-benzazepine, 2,3,4,5-tetrahydro-1H-2-benzazepine, 2,3-dihydro-1H-indole, etc.

Preferable ones of the condensed heterocyclic ring moiety in the above formulae shown by the formula:

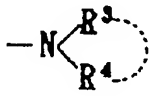


include the N-containing condensed heterocyclic rings shown by the following formulae:



wherein R^1 is of the same meaning as defined above. In the above formulae, preferable examples of R^1 include H, C_{1-4} alkyl groups (e.g. methyl, ethyl, n-propyl, i-propyl etc.), phenyl-C_{1-3} alkyl groups which may be substituted by a C_{1-4} alkoxy (e.g. phenylmethyl, (4-methoxyphenyl)methyl, phenylethyl, phenylpropyl, etc.) or C_{1-3} alkyl-carbonyl (e.g. acetyl, etc.), etc.

Referring to n, when the group of the formula:

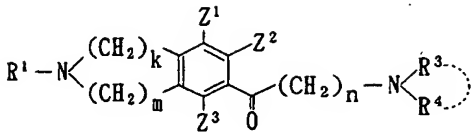


does not form a heterocyclic group, it is preferably a whole number of 3 to 8, and, when the group forms a heterocyclic group, it is preferably a whole number of 2 to 5.

As X^1, R^1-N< is preferable.

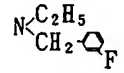
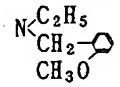
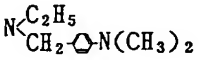
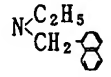
More specifically, the following compounds and salts thereof belonging to the compounds of the formula (I) or salts thereof are preferable.

[Table 1]



No.	R^1	k	m	n	Z^1	Z^2	Z^3	$N\langle^{R^3}_{R^4}$
1	H	0	2	2	H	H	H	$N\langle^{C_2H_5}_{H}$
2	H	0	2	2	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
3	H	0	2	3	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
4	H	0	2	4	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
5	H	0	2	5	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
6	H	0	2	6	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
7	H	0	2	7	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
8	H	0	2	8	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
9	Ac	0	2	6	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
10	COPh	0	2	6	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
11	CH_3	0	2	6	Cl	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
12	CH_2Ph	0	2	6	H	OH	H	$N\langle^{C_2H_5}_{CH_2Ph}$
13	Ph	0	2	6	H	OCH_3	H	$N\langle^{C_2H_5}_{CH_2Ph}$
14	H	0	2	6	F	H	CH_3	$N\langle^{C_2H_5}_{CH_2Ph}$
15	CH_2Ph	0	2	6	NO_2	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
16	H	0	2	6	H	H	H	$N\langle^{C_2H_5}_{CH_2}$-⟨⟩-OH

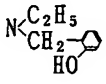
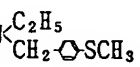
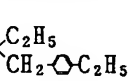
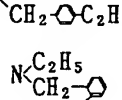
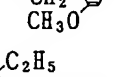
[Table 2]

No.	R^1	k	m	n	Z^1	Z^2	Z^3	$N<^{R^3}_{R^4}$
17	H	0	2	6	H	H	H	
18	H	0	2	6	H	H	H	
19	Ac	0	2	6	H	H	H	
20	H	0	2	6	H	H	H	
21	H	0	3	1	H	H	H	$N<^{CH_3}_{CH_2Ph}$
22	H	0	3	2	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
23	H	0	3	3	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
24	H	0	3	4	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
25	H	0	3	5	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
26	H	0	3	6	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
27	H	0	3	7	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
28	H	0	3	8	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
29	Ac	0	3	6	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
30	COPh	0	3	6	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
31	CH_3	0	3	6	Cl	H	H	$N<^{C_2H_5}_{CH_2Ph}$
32	CH_2Ph	0	3	6	H	OH	H	$N<^{C_2H_5}_{CH_2Ph}$
33	Ph	0	3	6	H	OCH_3	H	$N<^{C_2H_5}_{CH_2Ph}$
34	H	0	3	6	F	H	CH_3	$N<^{C_2H_5}_{CH_2Ph}$

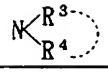
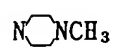
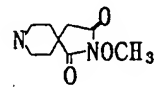
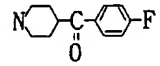
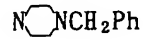
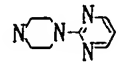
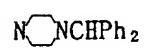
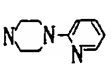
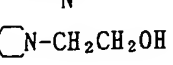
[Table 3]

No.	R^1	k	m	n	Z^1	Z^2	Z^3	$N<^{R^3}_{R^4}$
35	CH_2Ph	0	3	6	NO_2	H	H	$N<^{C_2H_5}_{CH_2Ph}$
36	H	0	3	6	H	H	H	$N<^{CH_3}_{CH_2-C_6H_3(CH_3O)}$
37	H	0	3	6	H	H	H	$N<^{C_2H_5}_{CH_2-C_6H_4-Cl}$
38	H	0	3	6	H	H	H	$N<^{C_2H_5}_{CH_2-C_6H_4-F}$
39	Ac	0	3	6	H	H	H	$N<^{C_2H_5}_{CH_2-C_6H_4-NO_2}$
40	H	0	3	6	H	H	H	$N<^{C_2H_5}_{CH_2-C_6H_4-CH_3}$
41	H	0	4	5	H	H	OH	$N<^{C_2H_5}_{CH_2Ph}$
42	H	0	4	6	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
43	CH_2Ph	0	4	6	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
44	CH_3	0	4	6	F	H	H	$N<^{CH(CH_3)_2}_{CH_2Ph}$
45	Ac	0	4	7	H	H	CH_3	$N<^{C_2H_5}_{CH_2Ph}$
46	H	0	5	5	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
47	H	0	5	6	Cl	H	H	$N<^{C_2H_5}_{CH_2Ph}$
48	H	0	5	6	H	OCH_3	H	$N<^{C_2H_5}_{CH_2Ph}$
49	Ac	0	5	6	H	H	H	$N<^{CH_2CH_2OH}_{CH_2Ph}$
50	COPh	0	5	7	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
51	C_2H_5	1	1	6	Cl	H	H	$N<^{C_2H_5}_{CH_2Ph}$
52	CH_2Ph	1	1	6	H	OH	H	$N<^{C_2H_5}_{CH_2Ph}$

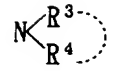
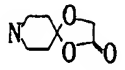
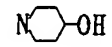
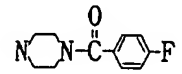
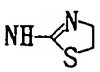
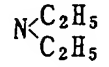
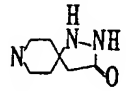
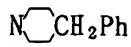
[Table 4]

No.	R^1	k	m	n	Z^1	Z^2	Z^3	$N<^{R^3}_{R^4}$
53	Ph	1	2	6	H	OCH_3	H	
54	H	1	2	6	F	H	CH_3	
55	CH_2Ph	1	2	6	NO_2	H	H	
56	H	1	2	6	H	H	H	
57	H	1	2	6	H	H	H	
58	H	1	3	6	F	H	H	$N<^{C_2H_5}_{CH_2Ph}$
59	Ac	1	3	6	H	H	H	$N<^{CH_3}_{CH_2Ph}$
60	CH_2Ph	1	3	6	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
61	H	2	2	5	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
62	H	2	2	6	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
63	Ac	2	2	6	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
64	CH_3	2	2	6	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
65	COPh	2	2	6	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
66	CO_2CH_3	2	2	7	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
67	Ac	2	2	1	H	H	H	
68	CH_2Ph	2	2	6	H	H	H	
69	CH_2Ph	2	2	7	H	H	H	
70	CH_2Ph	2	2	8	H	H	H	

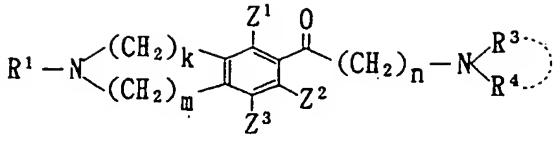
[Table 5]

No.	R^1	k	m	n	Z^1	Z^2	Z^3	
71	CH_2Ph	2	2	2	H	H	H	
72	CH_2Ph	2	2	2	H	H	H	
73	CH_2Ph	2	2	2	OCH_3	OCH_3	H	
74	CH_2Ph	2	2	2	F	H	CH_3	NH_2
75	CH_2Ph	2	2	2	H	H	H	
76	CH_2Ph	2	2	2	H	H	CH_3	
77	CH_2Ph	2	2	2	NO_2	OH	H	
78	CH_2Ph	2	2	2	H	H	H	
79	CH_2Ph	2	2	2	H	H	H	
80	CH_2- 	2	2	2	OCH_3	H	H	
81	Ac	2	2	3	H	H	H	
82	CH_2Ph	2	2	3	H	H	H	
83	CH_2Ph	2	2	3	H	H	H	
84	CH_2Ph	2	2	3	CH_3	H	H	
85	CH_2Ph	2	2	3	Cl	H	H	
86	CH_2- 	2	2	3	H	H	H	
87	CH_2- 	2	2	3	H	H	H	
88	CH_2- 	2	2	3	F	H	H	
89	CH_2- 	2	2	3	H	H	H	
90		2	2	3	OCH_3	H	H	

[Table 6]

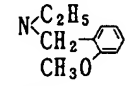
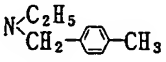
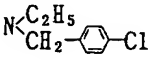
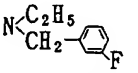
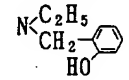
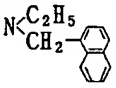
No.	R^1	k	m	n	Z^1	Z^2	Z^3	
91	CH_2Ph	2	2	4	H	H	H	
92	CH_2Ph	2	2	4	CH_3	OH	H	
93	CH_2Ph	2	2	4	OCH_3	H	H	
94	CH_2Ph	2	2	4	F	H	CH_3	
95	CH_2Ph	2	2	4	NO_2	H	H	
96	CH_2Ph	2	2	5	H	H	H	
97	CH_2Ph	2	2	5	H	H	H	
98	CH_2Ph	2	2	5	CH_3	H	H	
99	CH_2Ph	2	2	5	Cl	H	OH	
100	CH_2Ph	2	2	5	F	H	H	

[Table 7]

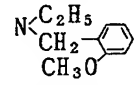
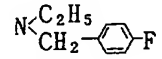
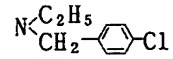
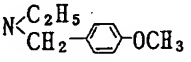
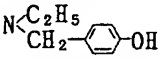


No.	R^1	k	m	n	Z^1	Z^2	Z^3	$N\langle^{R^3}_{R^4}$
101	H	0	3	1	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
102	H	0	3	2	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
103	H	0	3	3	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
104	H	0	3	4	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
105	H	0	3	5	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
106	H	0	3	6	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
107	H	0	3	7	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
108	H	0	3	8	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
109	Ac	0	3	6	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
110	COPh	0	3	6	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$

[Table 8]

No.	R^1	k	m	n	Z^1	Z^2	Z^3	$N\langle^{R^3}_{R^4}$
111	CH_3	0	3	6	Cl	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
112	CH_2Ph	0	3	6	H	OH	H	$N\langle^{C_2H_5}_{CH_2Ph}$
113	Ph	0	3	6	H	OCH_3	H	$N\langle^{C_2H_5}_{CH_2Ph}$
114	H	0	3	6	F	H	CH_3	$N\langle^{C_2H_5}_{CH_2Ph}$
115	CH_2Ph	0	3	6	H	H	NO_2	
116	H	0	3	6	H	H	H	
117	H	0	3	6	H	H	H	
118	H	0	3	6	H	H	H	
119	Ac	0	3	6	H	H	H	
120	H	0	3	6	H	H	H	
121	H	0	4	1	H	H	H	$N\langle^{CH_3}_{CH_2Ph}$
122	H	0	4	2	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
123	H	0	4	3	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
124	H	0	4	4	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
125	H	0	4	5	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
126	H	0	4	6	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
127	H	0	4	7	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
128	H	0	4	8	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$
129	Ac	0	4	6	H	H	H	$N\langle^{C_2H_5}_{CH_2Ph}$

[Table 9]

No.	R^1	k	m	n	Z^1	Z^2	Z^3	$N<^{R^3}_{R^4}$
130	COPh	0	4	6	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
131	CH_3	0	4	6	Cl	H	H	$N<^{C_2H_5}_{CH_2Ph}$
132	CH_2Ph	0	4	6	H	OH	H	$N<^{C_2H_5}_{CH_2Ph}$
133	Ph	0	4	6	H	OCH_3	H	$N<^{C_2H_5}_{CH_2Ph}$
134	H	0	4	6	F	H	CH_3	$N<^{C_2H_5}_{CH_2Ph}$
135	CH_2Ph	0	4	6	NO_2	H	H	$N<^{C_2H_5}_{CH_2Ph}$
136	H	0	4	6	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
137	H	0	4	6	H	H	H	
138	CO_2Ph	0	4	6	H	H	H	
139	Ac	0	4	6	H	H	H	
140	$CONHCH_3$	0	4	6	H	H	H	
141	H	0	5	4	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
142	H	0	5	5	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
143	H	0	5	6	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
144	H	0	5	6	H	H	H	
145	CH_3	0	5	6	H	OH	H	$N<^{C_2H_5}_{CH_2Ph}$
146	CH_2Ph	0	5	6	H	OCH_3	H	$N<^{C_2H_5}_{CH_2Ph}$
147	Ac	0	5	6	H	H	Cl	$N<^{C_2H_5}_{CH_2Ph}$
148	$CONHCH_3$	0	5	6	F	H	H	$N<^{C_2H_5}_{CH_2Ph}$
149	H	0	5	7	H	OCH_3	OCH_3	$N<^{C_2H_5}_{CH_2Ph}$

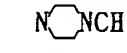
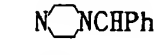
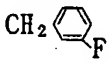
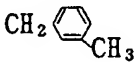
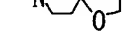
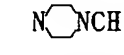
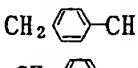
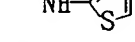
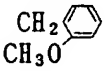
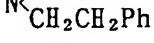
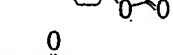
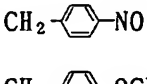
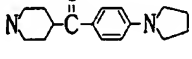
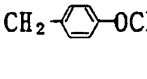
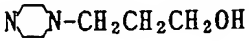
[Table 10]

No.	R^1	k	m	n	Z^1	Z^2	Z^3	$N<^{R^3}_{R^4}$
150	COPh	0	5	8	H	H	H	$N<^{CH_2CH_2OH}_{CH_2Ph}$
151	H	0	2	3	Cl	H	H	$N<^{CH_3}_{CH_2Ph}$
152	CH_2Ph	0	2	4	H	OH	H	$N<^{C_2H_5}_{CH_2Ph}$
153	Ph	0	2	6	H	OCH_3	H	$N<^{CH_2CH_2OH}_{CH_2Ph}$
154	H	0	2	6	F	H	CH_3	$N<^{C_2H_5}_{CH_2Ph}$
155	CH_2Ph	0	2	6	H	H	H	$N<^{CH_3}_{CH_2Ph}$
156	CH_2Ph	1	2	2	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
157	CH_2Ph	1	2	3	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
158	CH_2Ph	1	2	4	H	OH	H	$N<^{C_2H_5}_{CH_2Ph}$
159	Ac	1	2	5	H	OH_3	H	$N<^{C_2H_5}_{CH_2Ph}$
160	H	1	2	6	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
161	H	1	3	2	H	H	H	$N<^{CH_3}_{CH_2Ph}$
162	H	1	3	2	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$

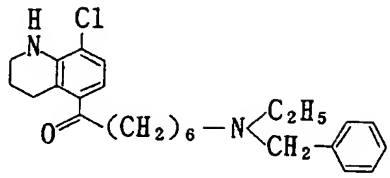
[Table 11]

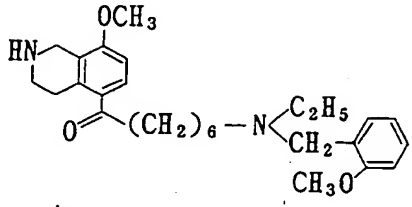
No.	R^1	k	m	n	Z^1	Z^2	Z^3	$N<^{R^3}_{R^4}$
163	H	1	3	3	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
164	H	1	3	4	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
165	H	1	3	5	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
166	H	1	3	6	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
167	H	1	3	7	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
168	H	1	3	8	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
169	Ac	1	3	6	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
170	COPh	1	3	6	H	H	H	$N<^{C_2H_5}_{CH_2Ph}$
171	CH_3	1	3	6	Cl	H	H	$N<^{C_2H_5}_{CH_2Ph}$
172	CO_2CH_3	1	3	6	H	OH	H	$N<^{C_2H_5}_{CH_2Ph}$
173	Ph	1	3	6	H	OCH_3	H	$N<^{C_2H_5}_{CH_2Ph}$
174	H	1	3	4	F	H	CH_3	$N<^{C_2H_5}_{CH_2Ph}$
175	C_2H_5	1	3	5	NO_2	H	H	$N<^{C_2H_5}_{CH_2}$-C$_6$H$_4$-F
176	H	1	3	6	H	H	CH_3	$N<^{C_2H_5}_{CH_2}$-C$_6$H$_4$-CH_3O
177	H	1	3	6	H	H	OCH_3	$N<^{C_2H_5}_{CH_2}$-C$_6$H$_4$-NO_2
178	H	1	3	6	H	H	H	$N<^{C_2H_5}_{CH_2}$-C$_6$H$_4$-NHAc
179	Ac	1	3	6	H	H	H	$N<^{C_2H_5}_{CH_2}$-C$_6$H$_4$-SCH_3
180	H	1	3	6	H	H	H	$N<^{C_2H_5}_{CH_2}$-C$_6$H$_4$-CO_2CH_3
181	CH_2Ph	1	3	5	H	H	H	N⬡

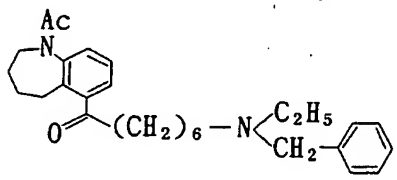
[Table 12]

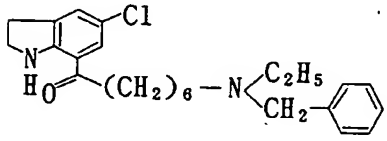
No.	R^1	k	m	n	Z^1	Z^2	Z^3	NR^3R^4
182	CH_2Ph	1	3	5	H	H	H	
183	CH_2Ph	1	3	6	H	H	H	
184	CH_2Ph	1	3	7	H	H	H	
185	CH_2Ph	1	3	8	H	H	H	
186	CH_2Ph	1	3	2	H	H	H	
187	CH_2Ph	1	3	2	H	H	H	
188	CH_2Ph	1	3	2	H	OCH_3	OCH_3	
189		1	3	2	H	H	H	
190		1	3	2	H	H	H	
191	CH_2Ph	1	3	3	H	H	H	
192	CH_2Ph	1	3	3	H	H	H	
193	CH_2Ph	1	3	3	H	OCH_3	H	
194		1	3	3	H	H	CH_3	
195		1	3	3	H	H	NO_2	
196	CH_2Ph	1	3	4	H	H	H	
197	CH_2Ph	1	3	4	H	H	H	
198	CH_2Ph	1	3	4	H	H	H	
199		1	3	4	H	CH_3	CH_3	
200		1	3	4	H	H	OCH_3	

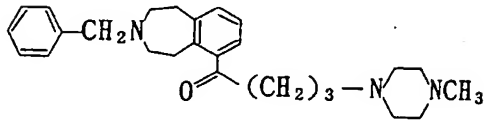
[Table 13]

201 

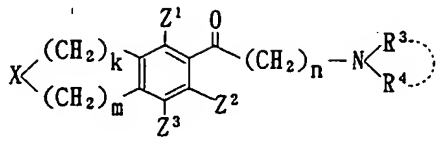
202 

203 

204 

205 

[Table 14]

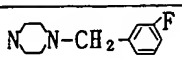
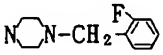
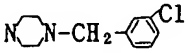
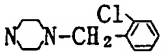
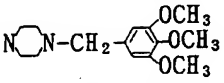
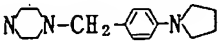
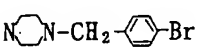
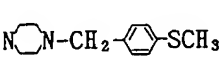
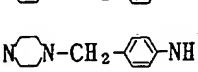
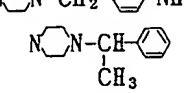
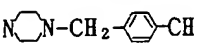
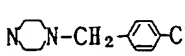
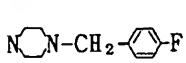
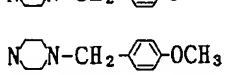
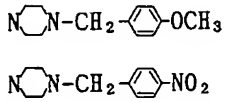
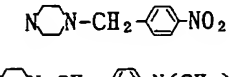
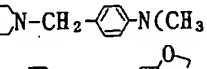
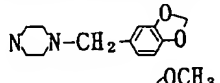
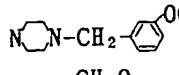
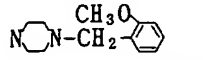


No.	X	k	m	n	Z^1	Z^2	Z^3	$N(R^3)(R^4)$
206	NH	2	2	2	H	H	H	N◯N-CH_2Ph
207	NAc	2	2	2	H	H	H	N◯N-CH_2Ph
208	NCOPh	2	2	2	H	H	H	N◯N-CH_2Ph
209	NCH_3	2	2	2	H	H	H	N◯N-CH_2Ph
210	NC_2H_5	2	2	2	H	H	H	N◯N-CH_2Ph
211	$NCH(CH_3)_2$	2	2	2	H	H	H	N◯N-CH_2Ph
212	NC_3H_7	2	2	2	H	H	H	N◯N-CH_2Ph
213	$NCHPh_2$	2	2	2	H	H	H	N◯N-CH_2Ph
214	$NCONHCH_3$	2	2	2	H	H	H	N◯N-CH_2Ph
215	NSO_2Ph	2	2	2	H	H	H	N◯N-CH_2Ph
216	NSO_2CH_3	2	2	2	H	H	H	N◯N-CH_2Ph
217	NCH_2-◯-CH_3	2	2	2	H	H	H	N◯N-CH_2Ph
218	NCH_2-◯-OCH_3	2	2	2	H	H	H	N◯N-CH_2Ph
219	NCH_2-◯-Cl	2	2	2	H	H	H	N◯N-CH_2Ph
220	NCH_2-◯-F	2	2	2	H	H	H	N◯N-CH_2Ph

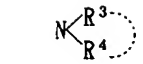
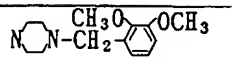
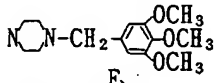
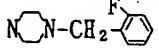
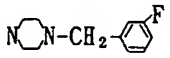
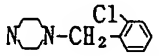
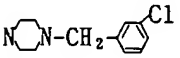
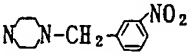
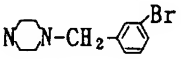
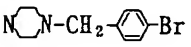
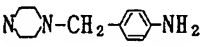
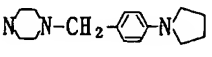
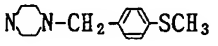
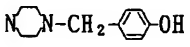
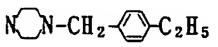
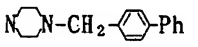
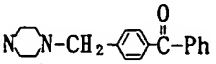
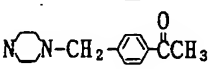
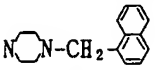
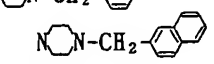
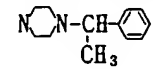
[Table 15]

No.	X	k	m	n	Z^1	Z^2	Z^3	$N\langle^{R^3}_{R^4}$
221	NCH_2-Ph-NO_2	2	2	2	H	H	H	N-Pip-$N-CH_2Ph$
222	NCH_2-Ph-NH_2	2	2	2	H	H	H	N-Pip-$N-CH_2Ph$
223	NCH_2-Ph-$N(CH_3)_2$	2	2	2	H	H	H	N-Pip-$N-CH_2Ph$
224	NCH_2-Ph(Cl)	2	2	2	H	H	H	N-Pip-$N-CH_2Ph$
225	NCH_2-Ph(Cl)	2	2	2	H	H	H	N-Pip-$N-CH_2Ph$
226	NCH_2-Ph(OCH_3)	2	2	2	H	H	H	N-Pip-$N-CH_2Ph$
227	NCH_2-Ph(CH_3O)	2	2	2	H	H	H	N-Pip-$N-CH_2Ph$
228	NCH_2-Ph(OCH_3)(OCH_3)	2	2	2	H	H	H	N-Pip-$N-CH_2Ph$
229	NCH_2-Ph-SCH_3	2	2	2	H	H	H	N-Pip-$N-CH_2Ph$
230	NCH_2-Ph-OH	2	2	2	H	H	H	N-Pip-$N-CH_2Ph$
231	NH	2	2	2	H	H	H	N-Pip-$N-CH_2Ph$
232	NH	2	2	2	H	H	H	N-Pip-$N-CH_2$-Ph-CH_3
233	NH	2	2	2	H	H	H	N-Pip-$N-CH_2$-Ph-Cl
234	NH	2	2	2	H	H	H	N-Pip-$N-CH_2$-Ph-F
235	NH	2	2	2	H	H	H	N-Pip-$N-CH_2$-Ph-OCH_3
236	NH	2	2	2	H	H	H	N-Pip-$N-CH_2$-Ph-NO_2
237	NH	2	2	2	H	H	H	N-Pip-$N-CH_2$-Ph-$N(CH_3)_2$
238	NH	2	2	2	H	H	H	N-Pip-$N-CH_2$-Ph(O,O)
239	NH	2	2	2	H	H	H	N-Pip-$N-CH_2$-Ph(OCH_3)
240	NH	2	2	2	H	H	H	N-Pip-$N-CH_2$-Ph(OCH_3)

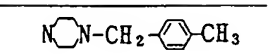
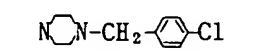
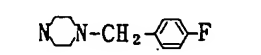
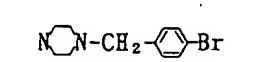
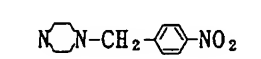
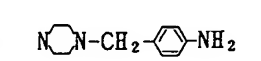
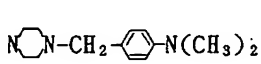
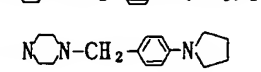
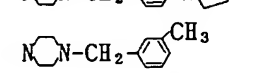
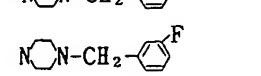
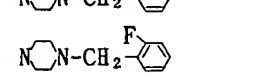
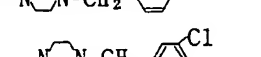
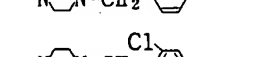
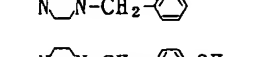
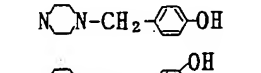
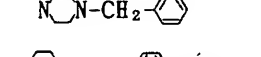
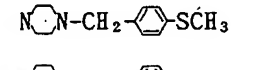
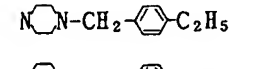
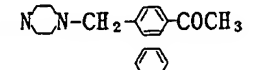
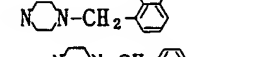
[Table 16]

No.	X	k	m	n	Z^1	Z^2	Z^3	$N<^{R^3}_{R^4}$
241	NH	2	2	2	H	H	H	
242	NH	2	2	2	H	H	H	
243	NH	2	2	2	H	H	H	
244	NH	2	2	2	H	H	H	
245	NH	2	2	2	H	H	H	
246	NH	2	2	2	H	H	H	
247	NH	2	2	2	H	H	H	
248	NH	2	2	2	H	H	H	
249	NH	2	2	2	H	H	H	
250	NH	2	2	2	H	H	H	
251	NCH_2Ph	2	2	2	H	H	H	
252	NCH_2Ph	2	2	2	H	H	H	
253	NCH_2Ph	2	2	2	H	H	H	
254	NCH_2Ph	2	2	2	H	H	H	
255	NCH_2Ph	2	2	2	H	H	H	
256	NCH_2Ph	2	2	2	H	H	H	
257	NCH_2Ph	2	2	2	H	H	H	
258	NCH_2Ph	2	2	2	H	H	H	
259	NCH_2Ph	2	2	2	H	H	H	
260	NCH_2Ph	2	2	2	H	H	H	

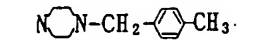
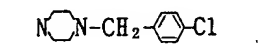
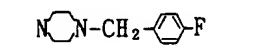
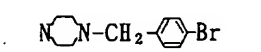
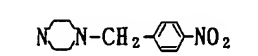
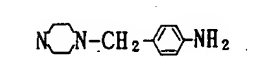
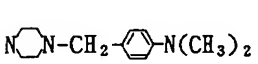
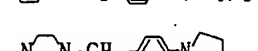
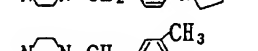
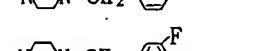
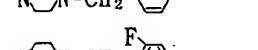
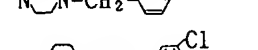
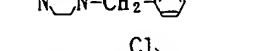
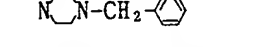
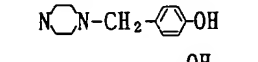
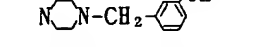
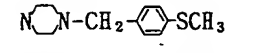
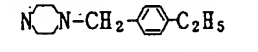
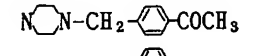
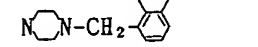
[Table 17]

No.	X	k	m	n	Z^1	Z^2	Z^3	
261	NCH_2Ph	2	2	2	H	H	H	
262	NCH_2Ph	2	2	2	H	H	H	
263	NCH_2Ph	2	2	2	H	H	H	
264	NCH_2Ph	2	2	2	H	H	H	
265	NCH_2Ph	2	2	2	H	H	H	
266	NCH_2Ph	2	2	2	H	H	H	
267	NCH_2Ph	2	2	2	H	H	H	
268	NCH_2Ph	2	2	2	H	H	H	
269	NCH_2Ph	2	2	2	H	H	H	
270	NCH_2Ph	2	2	2	H	H	H	
271	NCH_2Ph	2	2	2	H	H	H	
272	NCH_2Ph	2	2	2	H	H	H	
273	NCH_2Ph	2	2	2	H	H	H	
274	NCH_2Ph	2	2	2	H	H	H	
275	NCH_2Ph	2	2	2	H	H	H	
276	NCH_2Ph	2	2	2	H	H	H	
277	NCH_2Ph	2	2	2	H	H	H	
278	NCH_2Ph	2	2	2	H	H	H	
279	NCH_2Ph	2	2	2	H	H	H	
280	NCH_2Ph	2	2	2	H	H	H	

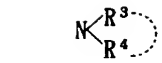
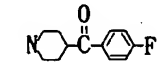
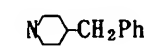
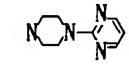
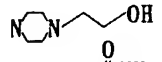
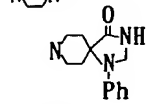
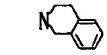
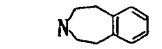
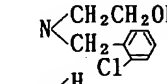
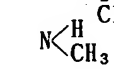
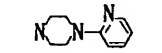
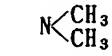
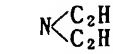
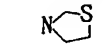
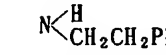
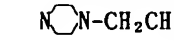
[Table 18]

No.	X	k	m	n	Z^1	Z^2	Z^3	$N\langle^{R^3}_{R^4}$
281	NAc	2	2	2	H	H	H	
282	NAc	2	2	2	H	H	H	
283	NAc	2	2	2	H	H	H	
284	NAc	2	2	2	H	H	H	
285	NAc	2	2	2	H	H	H	
286	NAc	2	2	2	H	H	H	
287	NAc	2	2	2	H	H	H	
288	NAc	2	2	2	H	H	H	
289	NAc	2	2	2	H	H	H	
290	NAc	2	2	2	H	H	H	
291	NAc	2	2	2	H	H	H	
292	NAc	2	2	2	H	H	H	
293	NAc	2	2	2	H	H	H	
294	NAc	2	2	2	H	H	H	
295	NAc	2	2	2	H	H	H	
296	NAc	2	2	2	H	H	H	
297	NAc	2	2	2	H	H	H	
298	NAc	2	2	2	H	H	H	
299	NAc	2	2	2	H	H	H	
300	NAc	2	2	2	H	H	H	

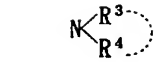
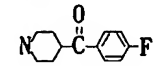
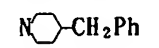
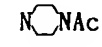
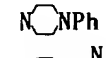
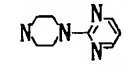
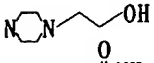
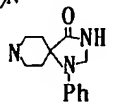
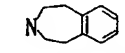
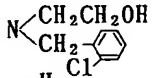
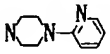
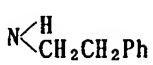
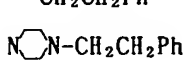
[Table 19]

No.	X	k	m	n	Z^1	Z^2	Z^3	$N\langle R^3 R^4$
301	NCH_3	2	2	2	H	H	H	
302	NCH_3	2	2	2	H	H	H	
303	NCH_3	2	2	2	H	H	H	
304	NCH_3	2	2	2	H	H	H	
305	NCH_3	2	2	2	H	H	H	
306	NCH_3	2	2	2	H	H	H	
307	NCH_3	2	2	2	H	H	H	
308	NCH_3	2	2	2	H	H	H	
309	NCH_3	2	2	2	H	H	H	
310	NCH_3	2	2	2	H	H	H	
311	NCH_3	2	2	2	H	H	H	
312	NCH_3	2	2	2	H	H	H	
313	NCH_3	2	2	2	H	H	H	
314	NCH_3	2	2	2	H	H	H	
315	NCH_3	2	2	2	H	H	H	
316	NCH_3	2	2	2	H	H	H	
317	NCH_3	2	2	2	H	H	H	
318	NCH_3	2	2	2	H	H	H	
319	NCH_3	2	2	2	H	H	H	
320	NCH_3	2	2	2	H	H	H	

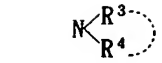
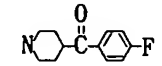
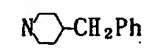
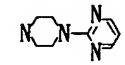
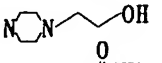
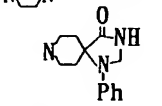
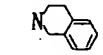
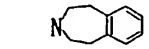
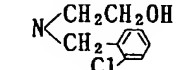
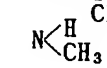
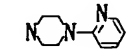
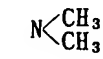
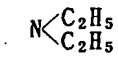
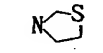
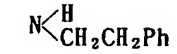
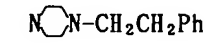
[Table 20]

No.	X	k	m	n	Z^1	Z^2	Z^3	
321	NH	2	2	2	H	H	H	
322	NH	2	2	2	H	H	H	
323	NH	2	2	2	H	H	H	
324	NH	2	2	2	H	H	H	
325	NH	2	2	2	H	H	H	
326	NH	2	2	2	H	H	H	
327	NH	2	2	2	H	H	H	
328	NH	2	2	2	H	H	H	
329	NH	2	2	2	H	H	H	
330	NH	2	2	2	H	H	H	
331	NH	2	2	2	H	H	H	
332	NH	2	2	2	H	H	H	
333	NH	2	2	2	H	H	H	
334	NH	2	2	2	H	H	H	
335	NH	2	2	2	H	H	H	NH_2
336	NH	2	2	2	H	H	H	
337	NH	2	2	2	H	H	H	
338	NH	2	2	2	H	H	H	
339	NH	2	2	2	H	H	H	
340	NH	2	2	2	H	H	H	

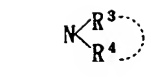
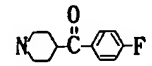
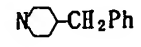
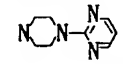
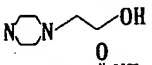
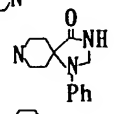
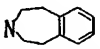
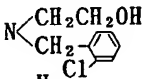
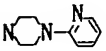
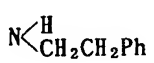
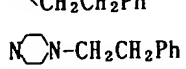
[Table 21]

No.	X	k	m	n	Z^1	Z^2	Z^3	
341	NAc	2	2	2	H	H	H	
342	NAc	2	2	2	H	H	H	
343	NAc	2	2	2	H	H	H	
344	NAc	2	2	2	H	H	H	
345	NAc	2	2	2	H	H	H	
346	NAc	2	2	2	H	H	H	
347	NAc	2	2	2	H	H	H	
348	NAc	2	2	2	H	H	H	
349	NAc	2	2	2	H	H	H	
350	NAc	2	2	2	H	H	H	
351	NAc	2	2	2	H	H	H	
352	NAc	2	2	2	H	H	H	
353	NAc	2	2	2	H	H	H	
354	NAc	2	2	2	H	H	H	
355	NAc	2	2	2	H	H	H	NH_2
356	NAc	2	2	2	H	H	H	
357	NAc	2	2	2	H	H	H	
358	NAc	2	2	2	H	H	H	
359	NAc	2	2	2	H	H	H	
360	NAc	2	2	2	H	H	H	

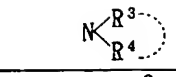
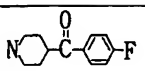
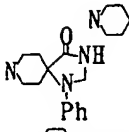
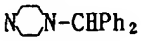
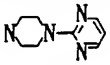
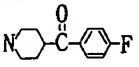
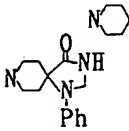
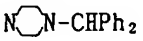
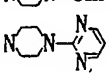
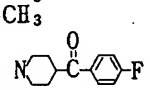
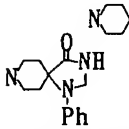
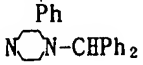
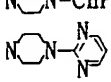
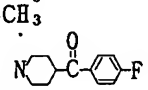
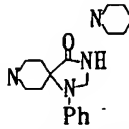
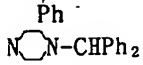
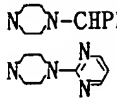
[Table 22]

No.	X	k	m	n	Z^1	Z^2	Z^3	
361	NCH_3	2	2	2	H	H	H	
362	NCH_3	2	2	2	H	H	H	
363	NCH_3	2	2	2	H	H	H	
364	NCH_3	2	2	2	H	H	H	
365	NCH_3	2	2	2	H	H	H	
366	NCH_3	2	2	2	H	H	H	
367	NCH_3	2	2	2	H	H	H	
368	NCH_3	2	2	2	H	H	H	
369	NCH_3	2	2	2	H	H	H	
370	NCH_3	2	2	2	H	H	H	
371	NCH_3	2	2	2	H	H	H	
372	NCH_3	2	2	2	H	H	H	
373	NCH_3	2	2	2	H	H	H	
374	NCH_3	2	2	2	H	H	H	
375	NCH_3	2	2	2	H	H	H	NH_2
376	NCH_3	2	2	2	H	H	H	
377	NCH_3	2	2	2	H	H	H	
378	NCH_3	2	2	2	H	H	H	
379	NCH_3	2	2	2	H	H	H	
380	NCH_3	2	2	2	H	H	H	

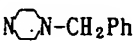
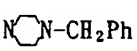
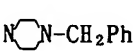
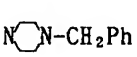
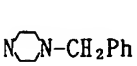
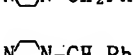
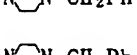
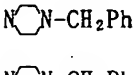
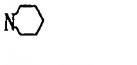
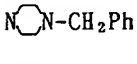
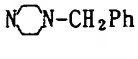
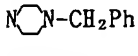
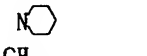
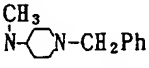
[Table 23]

No.	X	k	m	n	Z^1	Z^2	Z^3	
381	NCH_2Ph	2	2	2	H	H	H	
382	NCH_2Ph	2	2	2	H	H	H	
383	NCH_2Ph	2	2	2	H	H	H	
384	NCH_2Ph	2	2	2	H	H	H	
385	NCH_2Ph	2	2	2	H	H	H	
386	NCH_2Ph	2	2	2	H	H	H	
387	NCH_2Ph	2	2	2	H	H	H	
388	NCH_2Ph	2	2	2	H	H	H	
389	NCH_2Ph	2	2	2	H	H	H	
390	NCH_2Ph	2	2	2	H	H	H	
391	NCH_2Ph	2	2	2	H	H	H	
392	NCH_2Ph	2	2	2	H	H	H	
393	NCH_2Ph	2	2	2	H	H	H	
394	NCH_2Ph	2	2	2	H	H	H	
395	NCH_2Ph	2	2	2	H	H	H	NH_2
396	NCH_2Ph	2	2	2	H	H	H	
397	NCH_2Ph	2	2	2	H	H	H	
398	NCH_2Ph	2	2	2	H	H	H	
399	NCH_2Ph	2	2	2	H	H	H	
400	NCH_2Ph	2	2	2	H	H	H	

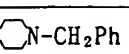
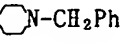
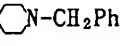
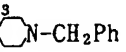
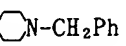
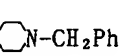
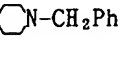
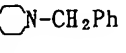
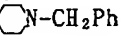
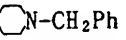
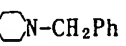
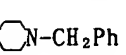
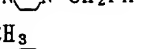
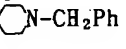
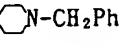
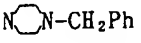
[Table 24]

No.	X	k	m	n	Z^1	Z^2	Z^3	
401	NCH_2Ph	2	2	3	H	H	H	
402	NCH_2Ph	2	2	3	H	H	H	
403	NCH_2Ph	2	2	3	H	H	H	
404	NCH_2Ph	2	2	3	H	H	H	
405	NCH_2Ph	2	2	3	H	H	H	
406	NCH_3	2	2	3	H	H	H	
407	NCH_3	2	2	3	H	H	H	
408	NCH_3	2	2	3	H	H	H	
409	NCH_3	2	2	3	H	H	H	
410	NCH_3	2	2	3	H	H	H	
411	NH	2	2	3	H	H	H	
412	NH	2	2	3	H	H	H	
413	NH	2	2	3	H	H	H	
414	NH	2	2	3	H	H	H	
415	NH	2	2	3	H	H	H	
416	NAc	2	2	3	H	H	H	
417	NAc	2	2	3	H	H	H	
418	NAc	2	2	3	H	H	H	
419	NAc	2	2	3	H	H	H	
420	NAc	2	2	3	H	H	H	

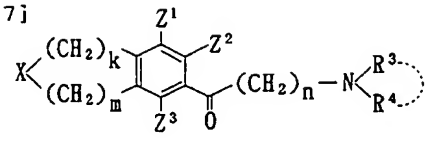
[Table 25]

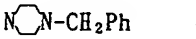
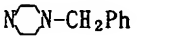
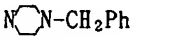
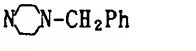
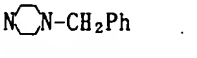
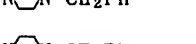
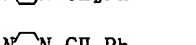
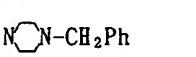
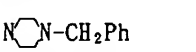
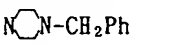
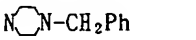
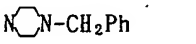
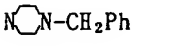
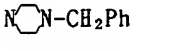
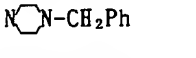
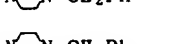
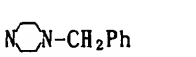
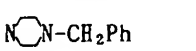
No.	X	k	m	n	Z^1	Z^2	Z^3	
421	NH	2	2	1	H	H	H	
422	NAc	2	2	1	H	H	H	
423	NCH_3	2	2	1	H	H	H	
424	NCH_2Ph	2	2	1	H	H	H	
425	NAc	2	2	1	H	H	H	
426	NCH_2Ph	2	2	1	H	H	H	
427	NH	2	2	3	H	H	H	
428	NAc	2	2	3	H	H	H	
429	NCH_3	2	2	3	H	H	H	
430	NCH_2Ph	2	2	3	H	H	H	
431	NAc	2	2	3	H	H	H	
432	NCH_2Ph	2	2	3	H	H	H	
433	NH	2	2	4	H	H	H	
434	NAc	2	2	4	H	H	H	
435	NCH_3	2	2	4	H	H	H	
436	NCH_2Ph	2	2	4	H	H	H	
437	NAc	2	2	4	H	H	H	
438	NCH_2Ph	2	2	4	H	H	H	
439	NAc	2	2	1	H	H	H	
440	NH	2	2	1	H	H	H	

[Table 26]

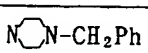
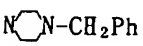
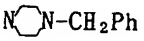
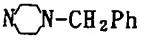
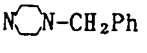
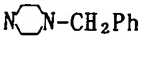
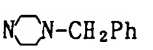
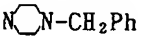
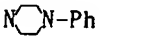
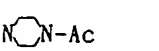
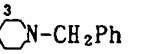
No.	X	k	m	n	Z^1	Z^2	Z^3	
441	NCH_2Ph	0	3	2	H	H	H	
442	NH	0	3	2	H	H	H	
443	$NCO_2C_2H_5$	0	3	2	H	H	H	
444	NAc	0	3	2	H	H	H	
445	NH	0	3	1	H	H	H	
446	NCH_2Ph	0	4	2	H	H	H	
447	NH	0	4	2	H	H	H	
448	$NCO_2C_2H_5$	0	4	2	H	H	H	
449	NAc	0	4	2	H	H	H	
450	NH	0	4	1	H	H	H	
451	NCH_2Ph	0	5	2	H	H	H	
452	NH	0	5	2	H	H	H	
453	$NCO_2C_2H_5$	0	5	2	H	H	H	
454	NAc	0	5	2	H	H	H	
455	NH	0	5	1	H	H	H	
456	NCH_2Ph	1	3	2	H	H	H	
457	NH	1	3	2	H	H	H	
458	$NCO_2C_2H_5$	1	3	2	H	H	H	
459	NAc	1	3	2	H	H	H	
460	NH	1	3	1	H	H	H	

[Table 27]

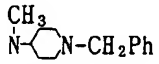
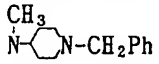
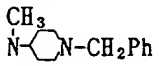
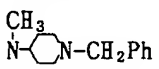
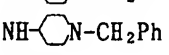
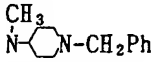
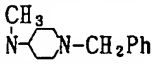
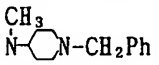
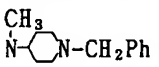
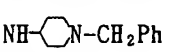
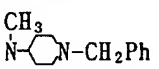
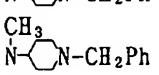
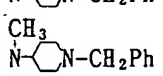
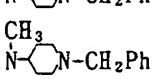
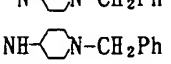
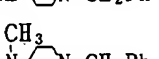
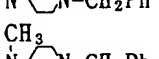
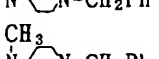
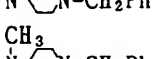
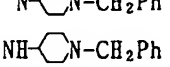


No.	X	k	m	n	Z^1	Z^2	Z^3	
461	NCH_2Ph	0	2	2	H	H	H	
462	NH	0	2	2	H	H	H	
463	NCH_3	0	2	2	H	H	H	
464	NAc	0	2	2	H	H	H	
465	$NCO_2C_2H_5$	0	2	2	H	H	H	
466	NCH_2Ph	0	3	2	H	H	H	
467	NH	0	3	2	H	H	H	
468	NCH_3	0	3	2	H	H	H	
469	NAc	0	3	2	H	H	H	
470	$NCO_2C_2H_5$	0	3	2	H	H	H	
471	NCH_2Ph	0	4	2	H	H	H	
472	NH	0	4	2	H	H	H	
473	NCH_3	0	4	2	H	H	H	
474	NAc	0	4	2	H	H	H	
475	$NCO_2C_2H_5$	0	4	2	H	H	H	
476	NCH_2Ph	1	3	2	H	H	H	
477	NH	1	3	2	H	H	H	
478	NCH_3	1	3	2	H	H	H	
479	NAc	1	3	2	H	H	H	
480	$NCO_2C_2H_5$	1	3	2	H	H	H	

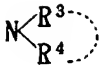
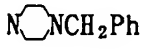
[Table 28]

No.	X	k	m	n	Z^1	Z^2	Z^3	
481	NCH_2Ph	1	2	2	H	H	H	
482	NH	1	2	2	H	H	H	
483	NCH_3	1	2	2	H	H	H	
484	NAc	1	2	2	H	H	H	
485	$NCO_2C_2H_5$	1	2	2	H	H	H	
486	O	0	2	2	H	H	H	
487	O	0	2	2	H	H	H	
488	O	0	2	2	H	H	H	
489	O	0	3	2	H	H	H	
490	O	0	3	2	H	H	H	
491	O	0	4	2	H	H	H	
492	O	0	4	2	H	H	H	
493	O	0	2	1	H	H	H	
494	S	0	2	2	H	H	H	
495	S	0	2	2	H	H	H	
496	S	0	3	2	H	H	H	
497	S	0	3	2	H	H	H	
498	S	0	4	2	H	H	H	
499	S	0	4	2	H	H	H	
500	S	0	3	1	H	H	H	

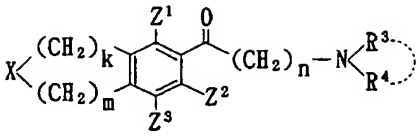
[Table 29]

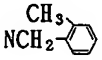
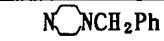
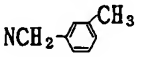
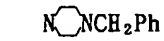
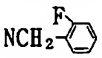
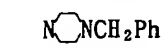
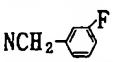
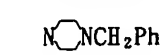
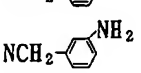
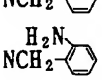
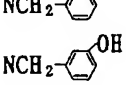
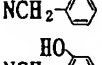
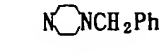
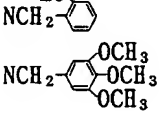
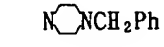
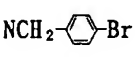
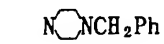
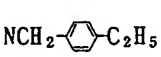
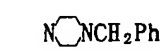
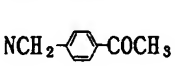
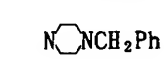
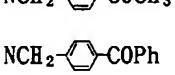
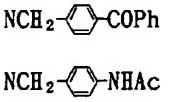
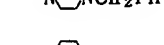
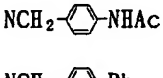
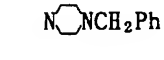
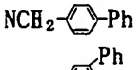
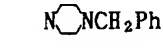
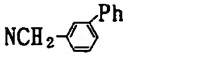
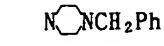
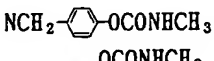
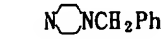
No.	X	k	m	n	Z^1	Z^2	Z^3	
501	NAc	0	2	1	H	H	H	
502	NH	0	2	1	H	H	H	
503	NCH_3	0	2	1	H	H	H	
504	NCH_2Ph	0	2	1	H	H	H	
505	NH	0	2	1	H	H	H	
506	NAc	0	3	1	H	H	H	
507	NH	0	3	1	H	H	H	
508	NCH_3	0	3	1	H	H	H	
509	NCH_2Ph	0	3	1	H	H	H	
510	NH	0	3	1	H	H	H	
511	NAc	0	4	1	H	H	H	
512	NH	0	4	1	H	H	H	
513	NCH_3	0	4	1	H	H	H	
514	NCH_2Ph	0	4	1	H	H	H	
515	NH	0	4	1	H	H	H	
516	NCH_2Ph	1	3	1	H	H	H	
517	NAc	1	3	1	H	H	H	
518	NCH_3	1	3	1	H	H	H	
519	NCH_2Ph	1	3	1	H	H	H	
520	NH	1	3	1	H	H	H	

[Table 30]

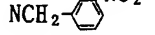
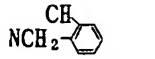
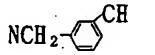
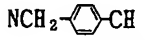
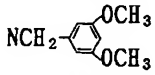
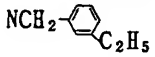
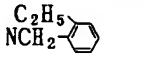
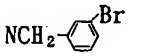
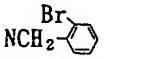
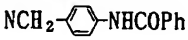
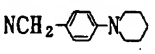
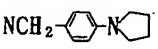
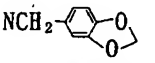
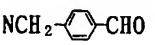
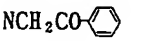
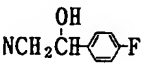
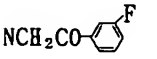
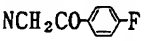
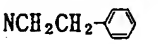
No.	X	k	m	n	Z^1	Z^2	Z^3	
521	NCH_2Ph	0	2	2	H	OH	H	
522	NCH_2Ph	0	2	2	H	OCH_3	H	
523	NCH_2Ph	0	3	2	H	OH	H	
524	NCH_2Ph	0	3	2	H	OCH_3	H	
525	NCHO	0	2	2	H	H	H	
526	NCHO	0	3	2	H	H	H	
527	NCH_2Ph	0	2	2	H	H	H	
528	NCH_2Ph	0	3	2	H	H	H	

[Table 31]

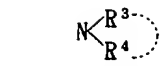
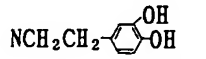
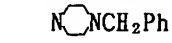
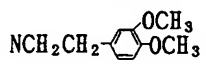
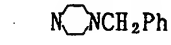
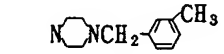
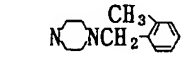
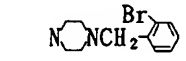
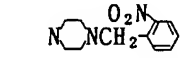
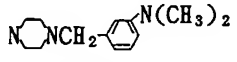
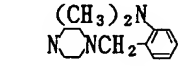
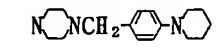
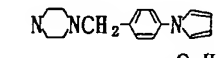
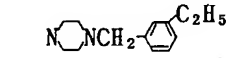
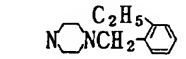
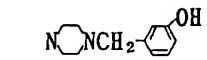


No.	X	k	m	n	Z^1	Z^2	Z^3	$N(R^3)(R^4)$
529		2	2	2	H	H	H	
530		2	2	2	H	H	H	
531		2	2	2	H	H	H	
532		2	2	2	H	H	H	
533		2	2	2	H	H	H	
534		2	2	2	H	H	H	
535		2	2	2	H	H	H	
536		2	2	2	H	H	H	
537		2	2	2	H	H	H	
538		2	2	2	H	H	H	
539		2	2	2	H	H	H	
540		2	2	2	H	H	H	
541		2	2	2	H	H	H	
542		2	2	2	H	H	H	
543		2	2	2	H	H	H	
544		2	2	2	H	H	H	
545		2	2	2	H	H	H	
546		2	2	2	H	H	H	

[Table 32]

No.	X	k	m	n	Z^1	Z^2	Z^3	
547		2	2	2	H	H	H	
548		2	2	2	H	H	H	
549		2	2	2	H	H	H	
550		2	2	2	H	H	H	
551		2	2	2	H	H	H	
552		2	2	2	H	H	H	
553		2	2	2	H	H	H	
554		2	2	2	H	H	H	
555		2	2	2	H	H	H	
556		2	2	2	H	H	H	
557		2	2	2	H	H	H	
558		2	2	2	H	H	H	
559		2	2	2	H	H	H	
560		2	2	2	H	H	H	
561		2	2	2	H	H	H	
562		2	2	2	H	H	H	
563		2	2	2	H	H	H	
564		2	2	2	H	H	H	
565		2	2	2	H	H	H	
566		2	2	2	H	H	H	

[Table 33]

No.	X	k	m	n	Z^1	Z^2	Z^3	
567		2	2	2	H	H	H	
568		2	2	2	H	H	H	
569	NCH_2Ph	2	2	2	H	H	H	
570	NCH_2Ph	2	2	2	H	H	H	
571	NCH_2Ph	2	2	2	H	H	H	
572	NCH_2Ph	2	2	2	H	H	H	
573	NCH_2Ph	2	2	2	H	H	H	
574	NCH_2Ph	2	2	2	H	H	H	
575	NCH_2Ph	2	2	2	H	H	H	
576	NCH_2Ph	2	2	2	H	H	H	
577	NCH_2Ph	2	2	2	H	H	H	
578	NCH_2Ph	2	2	2	H	H	H	
579	NCH_2Ph	2	2	2	H	H	H	
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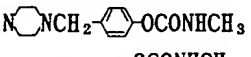
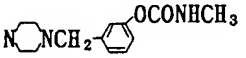
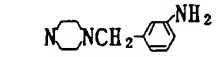
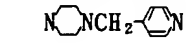
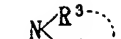
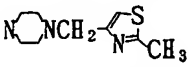
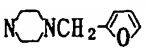
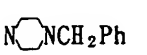
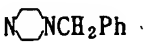
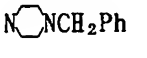
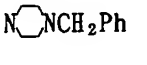
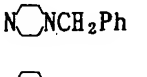
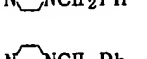
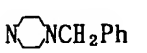
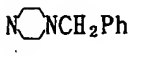
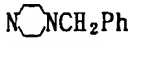
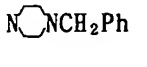
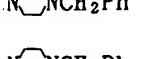
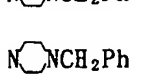
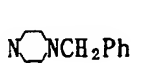
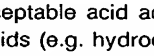
581	NCH_2Ph	2	2	2	H	H	H	
582	NCH_2Ph	2	2	2	H	H	H	
583	NCH_2Ph	2	2	2	H	H	H	
584	NCH_2Ph	2	2	2	H	H	H	
585	NCH_2Ph	2	2	2	H	H	H	
586	NCH_2Ph	2	2	2	H	H	H	

[Table 34]

No.	X	k	m	n	Z^1	Z^2	Z^3	
587	NCH_2Ph	2	2	2	H	H	H	
588	NCH_2Ph	2	2	2	H	H	H	
589	NCH_2Ph	2	2	2	H	OH	H	
590	NCH_2Ph	2	2	2	H	OCH_3	H	
591	NCH_2Ph	2	2	2	H	Cl	H	
592	NCH_2Ph	2	2	2	H	Br	H	
593	NCH_2Ph	2	2	2	H	CH_3	H	
594	NCH_2Ph	1	3	2	H	OH	H	
595	NCH_2Ph	1	3	2	H	OCH_3	H	
596	NCH_2Ph	0	3	2	H	OH	H	
597	NCH_2Ph	0	3	2	H	OCH_3	H	
598	NCHO	2	1	2	H	H	H	
599	NCHO	0	3	2	H	H	H	
600	NCHO	1	3	2	H	H	H	
601	NCHO	0	4	2	H	H	H	
602	NCHO	0	5	2	H	H	H	
603	NCH_2Ph	2	2	2	H	H	H	
604	NCH_2Ph	1	3	2	H	H	H	
605	NCH_2Ph	0	3	2	H	H	H	

In the tables, Ac stands for acetyl group, and Ph stands for phenyl group.

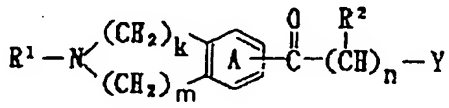
As salts of the compounds [I] and [VII] of this invention, physiologically acceptable acid addition salts are especially preferable. Examples of these salts include salts with inorganic acids (e.g. hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid), and salts with organic acids (e.g. acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid,

benzoic acid, methanesulfonic acid, benzenesulfonic acid). And, in the case where the compounds [I] and [VII] of this invention have an acid group such as -COOH, they may form salts with inorganic bases (e.g. an alkali metal or alkaline earth metal such as sodium, potassium, calcium, magnesium etc., ammonia) or organic bases (e.g. tri-C_{1-3} alkylamine such as triethylamine, etc.).

In the following, the process of producing the compound [I] or its salts of the present invention is described.

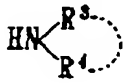
While the following description applies not only to the production of the compound [I] per se but also to the production of its salts, these compounds are simply referred to as the compound [I] inclusively in the description.

The compound [I] can be produced by, for example, reacting a compound represented by the formula:



[II]

wherein each symbol has the same meaning as defined above, or a salt thereof, with a compound represented by the formula:



[III]

wherein each symbol has the same meaning as defined above or a salt thereof.

As the leaving group shown by Y in the formula [II], use is made of, for example, halogen atoms (e.g. chlorine, bromine, iodine, etc.), C_{1-6} alkylsulfonyloxy (e.g. methanesulfonyloxy, ethanesulfonyloxy, etc.), C_{6-10} arylsulfonyloxy (e.g. benzenesulfonyloxy, p-toluenesulfonyloxy, etc.), etc. Among them, halogen atoms are preferable, more specifically, chlorine, bromine, etc.

As salts of the compound [II] and [III], use is made of, for example, salts with inorganic acids (e.g. hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid) or those with organic acids (e.g. acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid; benzoic acid, methanesulfonic acid, benzenesulfonic acid). And, in the case where the compounds [II] and [III] of this invention have an acid group such as -COOH, they may form salts with inorganic bases (e.g. an alkali metal or alkaline earth metal such as sodium, potassium, calcium, magnesium, etc., ammonia) or organic bases (e.g. tri-C_{1-3} alkylamine such as triethylamine, etc.).

The amount of the compound [III] or a salt thereof to be employed in this reaction ranges, usually, from 1.0 to 50.0 mol., preferably 1.0 to 10.0 mol., relative to one mol. of the compound [II] or a salt thereof. This reaction can be conducted at temperatures ranging from 0 °C to 120 °C. The reaction time ranges, usually, from 10 minutes to 48 hours, preferably from 2 to 16 hours.

While this reaction can be conducted in the absence of solvent, it can be conducted, upon necessity, in a solvent. As the solvent, any one can be employed unless it hampers the reaction, exemplified by lower alcohols such as methanol, ethanol, propanol, isopropanol, n-butanol, t-butanol, etc., ethers such as dioxane, ether, tetrahydrofuran, etc., aromatic hydrocarbons such as toluene, benzene, xylene, etc., amides such as dimethylformamide, dimethylacetamide, hexamethylphosphonotriamide, etc., esters such as ethyl acetate, butyl acetate, etc. The amount the solvent to be employed ranges, usually, from 0.5 to 100 ml, preferably from 5 to 20 ml, relative to 1 mmol.of the compound [II] or salt thereof.

This reaction can also be conducted in the presence of a base, when necessary. Examples of the base to be employed include inorganic bases such as sodium carbonate, potassium carbonate, lithium carbonate, sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, etc. and organic bases such as pyridine, 4-dimethylaminopyridine, triethylamine, etc. The amount of the base to be employed ranges, usually, from equimol. to excess amount, preferably from 1.0 to 5.0 mol. relative to one mol. of the compound [III] or a salt thereof.

It is also possible to promote this reaction by allowing an iodide (e.g. sodium iodide, potassium iodide, lithium iodide) to be present in the reaction system. The amount of the iodide to be employed ranges, usually from 1 to 5 mol., preferably 1.0 to 1.5 mol. relative to one mol. of the compound [II] or a salt thereof.

The compound [I], wherein R^1 stands for an optionally substituted hydrocarbon group or an optionally substituted acyl group, or a salt thereof can be produced by, for example, reacting a compound [I], wherein R^1 stands for H (R = H), or a salt thereof, with a compound represented by the formula

$R^{1'}$-Y^2 [VIII]

wherein $R^{1'}$ stands for an optionally substituted hydrocarbon group or an optionally substituted acyl group, and Y^2 stands for a leaving group, or a salt thereof.

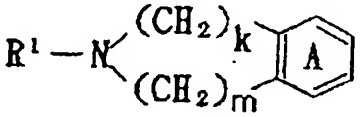
Examples of the salts of the compound [VIII] include those with inorganic acids (e.g. hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid) or organic acids (e.g. acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid). Further, in the case where the compound [VIII] of this invention has an acid group such as -COOH, the compound [VIII] may be in the form of salt with an inorganic base (e.g. an alkali metal or alkaline earth metal such as sodium, potassium, calcium, magnesium, etc., ammonia) or an organic base (e.g. tri-C_{1-3} alkylamine such as triethylamine, etc.).

As the leaving group shown by Y^2, use is made of, for example, a halogen atom (e.g. chlorine, bromine, iodine), C_{1-6} alkylsulfonyloxy (e.g. methanesulfonyloxy, ethanesulfonyloxy), C_{6-10} arylsulfonyloxy (e.g. benzenesulfonyloxy, p-toluenesulfonyloxy), etc. Especially, halogen atoms are preferable.

As the optionally substituted hydrocarbon groups shown by $R^{1'}$, use is made of, for example, the optionally substituted hydrocarbon groups shown by R^1 as described in the foregoing. As the optionally substituted acyl groups shown by $R^{1'}$, use is made of, for example, the optionally substituted acyl groups shown by R^1 as described in the foregoing.

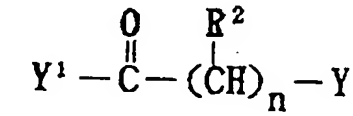
Further, the compound [I] (R = H) or a salt thereof can be produced also by subjecting a compound [I], wherein R^1 stands for an optionally substituted acyl group, or a salt thereof to hydrolysis with an acid or a base, in the same manner as in conventional hydrolysis.

The starting compound [II] or a salt thereof can be produced by reacting a compound represented by the formula:



[IX]

wherein each symbol has the same meaning as defined above, or a salt thereof, with a compound represented by the formula:



[X]

wherein Y^1 stands for a leaving group, and other symbols are of the same meanings as defined above.

As salts of the compound [IX], use is made of, for example, salts with an inorganic acid (e.g. hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid) or an organic acid (e.g. acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid). Further, in the case where the compound [IX] of this invention has an acid group such as -COOH, the compound [IX] may be in the form of a salt with an inorganic base (e.g. an alkali metal or an alkaline earth metal such as sodium, potassium, calcium, magnesium, etc., ammonia) or an organic base (e.g. tri-C_{1-3} alkylamine such as triethylamine, etc.).

As the leaving group shown by Y^1, use is made of, for example, halogen atoms (e.g. chlorine, bromine, iodine), C_{1-6} alkylsulfonyloxy (e.g. methanesulfonyloxy, ethanesulfonyloxy), C_{6-10} arylsulfonyloxy (e.g. benzenesulfonyloxy, p-toluenesulfonyloxy), etc. Especially, halogen atoms are preferable.

The compound [IX] or salts thereof can be produced in accordance with a per se known method or a method analogous thereto, for example, descriptions on J. Org. Chem. 34, 2235 (1969), J. Org Chem. 54, 5574 (1989), Tetrahedron Lett. 35, 3023 (1977), and Bull. Chem. Soc. Jpn. 56, 2300 (1983).

The compound [X] can be produced by a per se known method or a method analogous thereto.

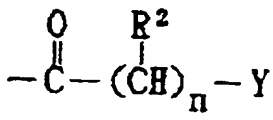
The reaction of the compound [IX] or a salt thereof with the compound [X] can be conducted by using, for example, usually about 1 to 20 mol., preferably about 1 to 5 mol., of the compound [X] or a salt thereof relative to 1 mol. of the compound [IX], in the presence of, for example, a Lewis acid.

This reaction can be conducted without using a solvent or, upon necessity, in a solvent. As the solvent, any one which is conventionally usable in chemical reactions, unless it hampers the reaction, can be employed, as exemplified by organic solvents including hydrocarbons (e.g. pentane, hexane, benzene, toluene, nitrobenzene, etc.), halogenated hydrocarbons (e.g. dichloromethane, chloroform, 1,2-dichloroethane, carbon tetrachloride, etc.), ethers (e.g. ethyl ether, tetrahydrofuran, dioxane, dimethoxyethane, etc.), nitro alkanes (e.g. nitromethane, propionitrile, etc.), and carbon disulfide. Especially, dichloromethane, 1,2-dichloroethane, nitrobenzene and carbon disulfide are preferable. The amount of the solvent ranges usually from 0.5 to 100 ml, preferably from 5 to 20 ml, relative to 1 mmol of the compound [IX] or a salt thereof.

The reaction temperature ranges usually from from about -30 • C to about 150 • C, preferably from about 20 • C to about 100 • C. The reaction time ranges usually from 0.5 to 72 hours, preferably from 1 to 16 hours.

And, as the Lewis acid to be employed in this reaction, use is made of, for example, aluminum chloride, zinc chloride, titanium chloride, tin(IV) chloride, boron trifluoride, iron(II) chloride, iron(III) chloride, antimony pentachloride (V), bismuth chloride (III), silver chloride (II), hydrogen fluoride, sulfuric acid, polyphosphoric acid, etc. Among them, aluminum chloride and the like are preferable. The amount of the Lewis acid to be employed ranges usually from 1 to 10 mol., preferably from 2 to 10 mol., relative to 1 mol. of the compound [IX] or a salt thereof.

In the above reaction, the position where the group of the compound [X]



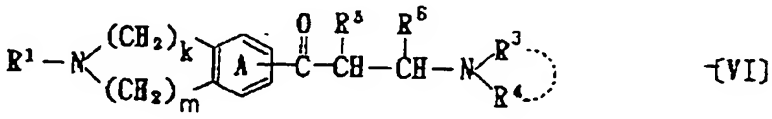
is introduced into the compound [IX] or a salt thereof may be any of the positions on ring A on which the substitution can take place. For example, in the case where the skeleton of the compound [IX] or a salt thereof is 1,2,3,4-tetrahydroquinoline (provided that the ring A is unsubstituted), the group of the compound [X] is introduced principally into 6-position, while such compounds as having the group introduced at any other positions (5-position, 7-position, 8-position) can be produced and separated as well.

The compound [II] or salts thereof obtained thus above can be isolated and refined by a conventional means such as concentration, pH change, phasic transfer, solvent extraction, fractional distillation, distillation, crystallization, recrystallization and chromatography, while they may be fed to the subsequent process as the material in the state of reaction mixture without isolation.

The stating compound [III] or salts thereof can be produced by a per se known method or a method analogous thereto.

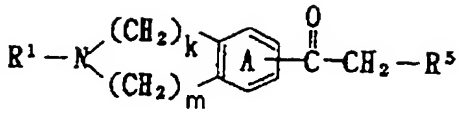
The compound [VIII] or salts thereof can be produced by a per se known method or a method analogous thereto.

And, among the compounds [I], those where n is 2, i.e. the compound of the formula:



[VI]

wherein each symbol is of the same meaning as defined above, or a salt thereof, can be produced also by reacting a compound of the formula:

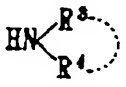


[IV]

wherein each symbol is of the same meaning as defined above, or a salt thereof, with a compound represented by the formula:

R^6-CHO [V]

wherein R^6 is of the same meaning as defined above and a compound represented by the formula:



[III]

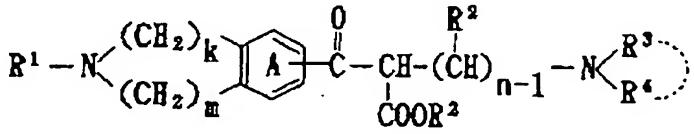
wherein each symbol is of the same meaning as defined above, or a salt thereof.

As salts of the compound [IV], use is made of, for example, those with inorganic acids (e.g. hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid) or with organic acids (e.g. acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid). Further, in the case where the compound [IV] of this invention has an acid group such as -COOH, the compound [IV] may be in the form of a salt with an inorganic base (e.g. alkali metal or alkaline earth metal such as sodium, potassium, calcium, magnesium, etc., ammonia) or with an organic base (e.g. tri-C_{1-3} alkylamine such as triethylamine, etc.).

This reaction can be conducted in substantially the same manner as Mannich reaction described in Organic Reaction, Vol. 1, p 303 to 341. More specifically, this reaction is conducted by reacting, for example, the compound [V] and the compound [III] or a salt thereof, with the compound [IV] or a salt thereof in a ratio of usually 0.9 to 10, preferably 1.0 to 3.0, equivalents of the former relative to 1 equivalent of the latter. Wile this reaction can be carried out usually at temperatures ranging from room temperature to under heating (10 to 150°C), it is conducted preferably at temperatures ranging from 80 to 120°C. The reaction time ranges usually from 1 to 48 hours, preferably from 2 to 24 hours. This reaction can usually be conducted in the absence or presence of solvent. As the solvent, any one to be used in general for Mannich reaction can be employed, unless it hampers this reaction. For example, alcohols such as ethanol are often employed. The amount of the solvent ranges usually from 0.5 to 200 ml, preferably from 5 to 40 ml, relative to 1 mmol. of the compound [IV] or a salt thereof. Further, this reaction can be conducted, when desired, in the presence of an inorganic acid such as hydrochloric acid. The acid is used in a catalytic amount relative to the compound [IV] or a salt thereof (0.001 to 0.05 equivalent relative to 1 equivalent of the compound [IV] or a salt thereof). In the case where the compound [III] or [IV] to be employed for the reaction is not in the form of salt, however, it is preferable to use the acid in an excess amount sufficient for allowing these compounds to form salts.

The compound [IV] or salts thereof and the compound [V] can be produced by a per se known method or a method analogous thereto.

Further, the compound [I] or a salt thereof can be produced also by first hydrolizing the ester moiety ($COOR^2$) of, for example, a compound represented by the formula:



[XI]

wherein each symbol is of the same meaning as defined above or a salt thereof, which can be obtained by the method described above, then by subjecting the reaction mixture to decarboxylation. The hydrolysis

and decarboxylation can be conducted in the same manner as per se known methods.

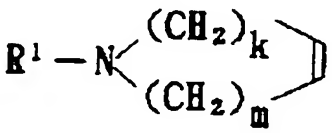
And, the compound [I] or a salt thereof can be produced also by subjecting, for example, a compound, wherein R^1 is carboxylic acid acyl, or a salt thereof to reduction in a conventional manner. In this reaction, it is preferable that, upon necessity, the functional group (e.g. ketone) of the compound [I] or a salt thereof (R^1 = carboxylic acid acyl group) is first protected, in the form of acetal with, for example, ethylene glycol or any other alcohol (e.g. methanol, ethanol, etc.), then the thus protected compound is subjected to reduction, and then the reaction mixture is subjected to deprotection with an acid or base or by heating.

And, in each of the above-mentioned reactions, in the case where the starting compound has, as substituents, amino group, carboxyl group, hydroxyl group, etc., these groups may be protected with such protecting groups as generally used in peptide chemistry, and the object compound can be obtained by, upon necessity, removing these protecting groups after the reaction.

As the protecting groups of amino group, use is made of, for example, formyl, optionally substituted C_{1-6} alkyl-carbonyl groups (e.g. acetyl, ethylcarbonyl, etc.), benzoyl, C_{1-6} alkyloxy-carbonyl (e.g. methoxy-carbonyl, ethoxycarbonyl, etc.), phenyloxycarbonyl (e.g. phenoxycarbonyl, etc.), C_{7-15} aralkyloxy-carbonyl (e.g. benzyloxycarbonyl, fluorenyloxycarbonyl, etc.), trityl, phthaloyl, etc. As substituents on these groups, use is made of halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.), C_{1-6} alkyl-carbonyl (e.g. methyl-carbonyl, ethylcarbonyl, butylcarbonyl, etc.), nitro group, among others, and the number of these substituents ranges from 1 to 3. As the protecting group of carboxyl group, use is made of, for example, an optionally substituted C_{1-6} alkyl (e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl, tert-butyl, etc.), phenyl, trityl, silyl, etc. As substituents on these groups, use is made of halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.), formyl, C_{1-6} alkyl carbonyl (e.g. methylcarbonyl, ethylcarbonyl, butylcarbonyl, etc.), nitro, etc., and the number of these substituents ranges from 1 to 3. As the group protecting hydroxyl group, use is made of, for example, an optionally substituted C_{1-6} alkyl (e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl, tert-butyl, etc.), phenyl, C_{7-10} aralkyl (e.g. benzyl, etc.), formyl, C_{1-6} alkyl carbonyl (e.g. acetyl, ethylcarbonyl, etc.), phenyloxycarbonyl, C_{7-10} aralkyl-carbonyl (e.g. benzyloxycarbonyl, etc.), pyranyl, furanyl, silyl, etc. As substituents on these groups, use is made of halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C_{1-6} alkyl, phenyl, C_{7-10} aralkyl, nitro group, etc., and the number of these substituents ranges from 1 to 4.

And, as the means of removing these protecting groups, use is made of per se known means or those analogous thereto, as exemplified by those which comprise processing with an acid, a base, reduction, UV-ray, hydrazine, phenyl hydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate, etc.

Further, the compound [VII] of this invention or salts thereof can be produced by substantially the same method as described above for the production of the compound [I] or salts thereof, using a compound wherein the group



in, for example, the starting compound [II], [IV], [IX] or a salt thereof, is a group

The compound [I] or salts thereof and the compound [VII] or salts thereof thus obtained above can be isolated and refined by conventional separating means such as recrystallization, distillation, chromatography, etc. In the case where the compound [I] and the compound [VII] obtained thus above are in the free form, they can be led to salts by per se conventional means or those analogous thereto. Conversely, when the compound [I] or [VII] is obtained in the form of salt, it can be led to the free compound or any other salt by per se conventional means or those analogous thereto.

The compound [I] or salts thereof and the compound [VII] or salts thereof include their stereoisomers due to the presence of asymmetric carbon atoms. These isomers can be resolved into corresponding optically active compounds by means of a conventional optical resolution.

The compound [I] or salts thereof and the compound [VII] or salts thereof of the present invention act on the central nervous system of mammals, have strong cholinesterase inhibitory activity, and exhibit excellent antiamnestic effects on various amnesia-inducing actions in man and animals (e.g. mice, etc.). Further, the compound [I] or salts thereof and the compound [VII] or salts thereof of the present invention have monoamine (e.g. norepinephrine, serotonin, etc.) reuptake inhibitory activity, and exhibit excellent antidepressant activity, etc. in man and animals (e.g. mice, etc.).

The compound [I] or salts thereof and the compound [VII] or salts thereof of the present invention are remarkably excellent in separation of effects on central nervous system from those on peripheral nervous system, as compared with physostigmine and, at the antiamnestic and antidepressant dose level, do not cause peripheral nervous system effects such as spasm, salivation, diarrhea, etc. or, if they do, only slightly. Moreover, they are characterized by a long duration of effects and low toxicity, ensuring a remarkably high efficacy when administered orally. The acute toxicity of the compound [I] or salts thereof and the compound [VII] or salts thereof of the present invention is not less than 100 mg/kg. Therefore, the compounds of this invention are useful as a safely administrable agent for improving the cerebral function of mammalian animals including human beings.

Diseases on which the compounds of this invention are effective include senile dementia, Alzheimer's diseases, Huntington's chorea, hyperkinesia and mania. The compounds of this invention can be used for the prophylaxis or therapy of these diseases. Further, the compounds of this invention can be also used for the prophylaxis or therapy of depression, hypobulia, affective disorders, lack of spontaneity, etc. which are symptoms related to the above-mentioned diseases.

The compounds of this invention are usually formulated with pharmaceutically acceptable carriers or excipients, which can be administered orally or non-orally to man and other mammalian animals. Such pharmaceutical preparations may be those for oral administration (e.g. powders, tablets, granules and capsules) and for non-oral administration (e.g. suppositories, injections). These pharmaceutical compositions can be prepared by per se known methods. While the dosage depends on the type and symptom of diseases to be treated, in the case of oral administration to general adult humans (60 kg body weight), it ranges from about 0.01 mg to about 50 mg, preferably from 0.1 to 30 mg, more preferably from 0.5 to 10 mg per day.

By the following working examples, reference examples, formulation examples and experimental examples, the present invention will be illustrated in more concrete manner, but they should by no means be construed as defining the metes and bounds of this invention.

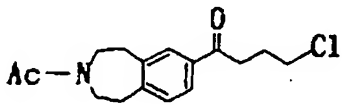
In the experimental examples and reference examples, elution in the procedure of column chromatography was carried out under observation by means of TLC (Thin Layer Chromatography) unless otherwise specified. In the TLC observation, $60F_{254}$ manufactured by Merck was employed as the TLC plate, the solvent employed as elution solvent for the column chromatography was employed as the developer, and a UV detector was employed for detection. As an adjunctive detection procedure, the spot on the TLC plate was sprayed with 48% HBr, heated to hydrolize, sprayed with a ninhydrin reagent and heated again, then the change to a red - reddish purple was regarded as positive reaction. The fractions containing the object compound were pooled. Unless otherwise specified, Merck Kieselgel 60 (70 to 230 mesh) was employed as the silica gel for the column.

Incidentally, the term "ambient temperature" or "room temperature" generally means usually temperatures ranging from about 5 • C to 40 • C, and the term "atmospheric pressure" means the neighborhood of one atmospheric pressure.

And, unless otherwise specified, % denotes percentage by weight.

Reference Example 1

4-Chloro-1-(3-acetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone



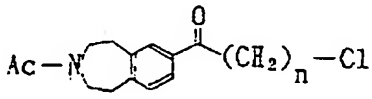
In 30 ml of dichloromethane, was dissolved 3.79 g of 3-acetyl-2,3,4,5-tetrahydro-1H-3-benzazepine. To the solution were added 3.38 g of 4-chlorobutyryl chloride and 4.00 g of aluminum chloride. The mixture was stirred for 2 hours at room temperature (about 20 • C). The reaction mixture was poured into 50 ml of ice-water. The organic layer was separated, which was washed successively with 50 ml of 0.5N aqueous solution of sodium hydroxide and 50 ml of pure water, then dried over anhydrous sodium sulfate. The solvent was distilled off to leave 5.40 g of an oily residue. The residue was purified by means of a silica gel column chromatography (developing solvent, ethyl acetate - dichloromethane 1:1 (V/V)) to afford 2.92 g of the title compound as colorless crystals, m.p.103-106 • C.

Elemental Analysis for $C_{16}H_{20}ClNO_2$:			
Calcd.:	C, 65.41;	H, 6.86;	N, 4.77
Found :	C, 65.33;	H, 6.91;	N, 4.69

Reference Example 2

By conducting substantially the same procedure as in Reference Example 1, compounds shown in Table 35 were obtained.

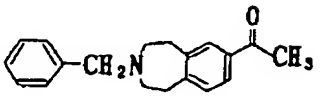
[Table 35]



Compound No.	n	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
1	1	128−130	$C_{14}H_{16}ClNO_2$	63.28	6.07	5.27
				(63.09	6.12	5.26)
2	2	123−124	$C_{15}H_{18}ClNO_2$	64.40	6.48	5.01
				(64.33	6.47	4.94)

Reference Example 3

7-Acetyl-3-(phenylmethyl)-2,3,4,5-tetrahydro-1H-3-benzazepine



To 7.36 g of 2,3,4,5-tetrahydro-1H-3-benzazepine and 10.37 g of potassium carbonate, was added 75 ml of ethanol. To the mixture, was added dropwise 8.38 g of benzyl bromide under ice-cooling in the course of 10 minutes, followed by stirring for 2 hours at 25 °C, then the solvent was distilled off. To the residue were added 100 ml of pure water and 100 ml of dichloromethane, then the organic layer was separated and dried over sodium sulfate, followed by distilling off the solvent to leave a crystalline residue.

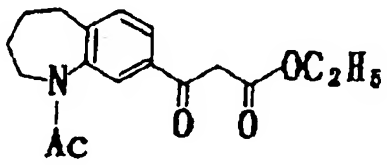
The residue was dissolved in 20 ml of methanol, to which was added 19 ml of 4N methanolic hydrochloric acid. Methanol was then distilled off, and the residue was suspended in 100 ml of ethyl acetate. Resulting crystals were collected by filtration, then the crystals were washed with 30 ml of ethyl acetate. The crystals were dried under reduced pressure to give 11.94 g of 3-(phenylmethyl)-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride.

10.95 g of the above-mentioned compound was dissolved in 80 ml of 1,2-dichloroethane, to which were added 10.67 g of aluminum chloride and 4.71 g of acetyl chloride, then the mixture was stirred for 30 minutes under reflux. The reaction mixture was poured into 150 ml of ice-water, then pH of the aqueous layer was adjusted to 10, followed by addition of 150 ml of dichloromethane. The organic layer was separated and dried over sodium sulfate. The solvent was then distilled off to leave 13.0 g of an oily residue. The residue was purified by means of a silica gel column chromatography (developing solvent, ethyl acetate - dichloromethane 1:2) to afford 10.44 g of the title compound as colorless crystals, m.p.89-91 °C.

Elemental Analysis for $C_{19}H_{21}NO$:			
Calcd.:	C, 81.68;	H, 7.58;	N, 5.01
Found :	C, 81.49;	H, 7.61;	N, 4.86

Reference Example 4

Ethyl β-(1-acetyl-2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)-β-oxopropionate



(1) To a solution of 18.9 g of 1-acetyl-2,3,4,5-tetrahydro-1H-1-benzazepine in 20 ml of carbon disulfide were first added 30.8 g of aluminum chloride then 7.8 ml of acetyl chloride gradually at room temperature. The mixture was heated for 16 hours under reflux. The reaction mixture was poured into ice water, which was subjected to extraction with dichloromethane. The extract solution was dried over anhydrous sodium sulfate, then the solvent was distilled off. The residue was purified by means of chromatography (developing solvent; dichloromethane - ethyl acetate = 5:1(V/V)) to give 13.5 g of pale yellow crystals. Recrystallization from diethyl ether - hexane affords 12.4 g of 1,8-diacetyl-2,3,4,5-tetrahydro-1H-1-benzazepineas colorless crystals, m.p.105-108 °C.

Elemental Analysis for $C_{14}H_{17}NO_2$:			
Calcd.:	C, 72.70;	H, 7.41;	N, 6.06
Found :	C, 72.82;	H, 7.36;	N, 6.00

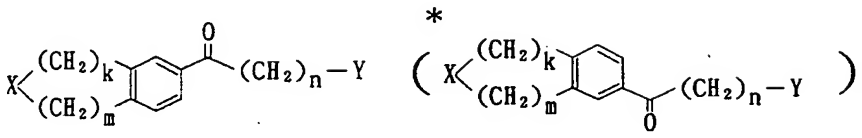
(2) To a refluxed solution of 3.83 g of diethyl carbonate and 1.04 g of sodium hydride (oil free) in 50 ml of tetrahydrofuran was added dropwise, under nitrogen atmosphere, a solution of 5 g of 1,8-diacetyl-2,3,4,5-tetrahydro-1H-1-benzazepine in 50 ml of tetrahydrofuran. The mixture was heated for 3 hours under reflux, then the reaction mixture was poured into ice-water, which was subjected to extraction with dichloromethane. The extract solution was dried over anhydrous sodium sulfate, then the solvent was distilled off. The residue was purified by means of chromatography (developing solvent; dichloromethane - ethyl acetate = 5:1(V/V)) to afford 3.5 g of the title compound as a colorless oily product.

Elemental Analysis for $C_{17}H_{21}NO_4$:			
Calcd.:	C, 67.31;	H, 6.98;	N, 4.62
Found :	C, 67.14;	H, 6.83;	N, 4.63

Reference Example 5

By substantially the same procedure as in Reference Example 1, compounds listed in Table 36 were obtained.

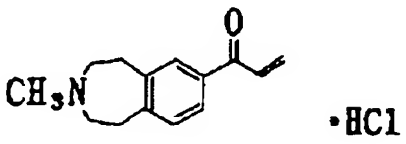
[Table 36]



Compound No.	X	k	m	n	Y	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
1	NAc	0	4	1	Cl	112-115	$C_{14}H_{16}ClNO_2$	63.28	6.07	5.27
								(63.11	6.14	5.33)
2	NAc	0	4	2	Cl	123-124	$C_{15}H_{18}ClNO_2$	64.40	6.49	5.01
								(64.35	6.56	4.91)
3	NCO_2Et	0	4	2	Cl	oil	$C_{16}H_{20}ClNO_3$	62.03	6.51	4.52
								(62.19	6.40	4.50)
4	NCH_2Ph	2	2	1	Cl	111-113	$C_{19}H_{20}ClNO$	72.72	6.42	4.46
								(72.50	6.45	4.44)
5	NCH_2Ph	2	2	2	Cl	176-178	$C_{20}H_{22}ClNO$ ·HCl	65.94	6.36	3.84
								(65.67	6.52	3.77)
6	NCH_2Ph	2	2	5	Br	oil	$C_{23}H_{28}BrNO$	66.67	6.81	3.38
								(66.57	6.83	3.37)
* 7	NCHO	2	0	2	Cl	134-136	$C_{12}H_{12}ClNO_2$	60.64	5.09	5.89
								(60.45	4.88	5.67)
8	NCHO	1	3	2	Cl	94- 96	$C_{14}H_{16}ClNO_2$	63.28	6.07	5.27
								(63.37	6.14	5.23)
9	NCHO	2	2	2	Cl	121-123	$C_{14}H_{16}ClNO_2$	63.28	6.07	5.27
								(63.17	6.02	5.31)
10	NAc	2	2	4	Cl	95- 98	$C_{17}H_{22}ClNO_2$	66.33	7.20	4.55
								(66.35	7.11	4.60)
11	NCO_2CH_3	2	2	2	Cl	117-120	$C_{15}H_{18}ClNO_3$	60.92	6.13	4.74
								(60.97	6.10	4.77)
*12	NCHO	3	0	2	Cl	103-105	$C_{13}H_{14}ClNO_2$	62.03	5.61	5.56
								(62.15	5.59	5.70)
13	NCHO	0	3	2	Cl	oil	$C_{13}H_{14}ClNO_2$	62.03	5.61	5.56
								(62.20	5.60	5.51)
14	NCHO	0	5	2	Cl	118-120	$C_{15}H_{18}ClNO_2$	64.40	6.48	5.01
								(64.48	6.43	5.14)
*15	NAc	3	0	2	Cl	75- 77	$C_{14}H_{16}ClNO_2$	63.28	6.07	5.27
								(63.20	6.04	5.26)
16	NAc	0	5	2	Cl	oil	$C_{16}H_{20}ClNO_2$	65.41	6.86	4.77
								(65.48	6.82	4.68)

Reference Example 6

1-(3-Methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)2-propen-1-one hydrochloride



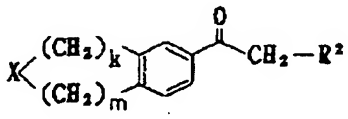
In 30 ml of 1,2-dichloroethane, was dissolved 1.28 g of 3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride. To the solution were added, at room temperature, 2.1 g of aluminum chloride and 0.66 ml of 3-chloropropionyl chloride, then the mixture was stirred for 2 hours. The reaction mixture was poured into 50 ml of ice-water, then the pH of the aqueous solution was adjusted to not lower than 9 with a 40% aqueous solution of sodium hdyroxide, followed by extraction with 50 ml of dichloromethane. The organic layer was washed with 50 ml of pure water, which was then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to give an oily residue, which was crystallized from dichloromethane-ether to afford 0.83 g of the title compound as pale yellow crystals, m.p.120-123 • C.

Elemental Analysis for $C_{14}H_{17}NO \cdot HCl \cdot H_2O$:			
Calcd.:	C, 62.33;	H, 7.47;	N, 5.19
Found :	C, 62.53;	H, 7.65;	N, 5.13

Reference Example 7

By substantially the same procedure as in Reference Example 1, the compounds shown in Table 37 were obtained.

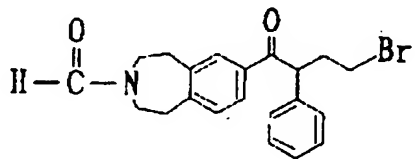
[Table 37]



Compound No.	X	k	m	R^2	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd.(Found) C	H	N
1	NCHO	2	2	Ph	140-142	$C_{19}H_{19}NO_2$	77.79	6.53	4.77
							(77.51	6.43	4.89)
2	NCH_2Ph	2	2	Ph	oil	$C_{25}H_{25}NO$	84.47	7.09	4.50
							(84.61	7.01	4.50)

Reference Example 8

4-Bromo-1-(3-formyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-2-phenyl-1-butanone



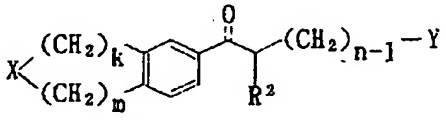
In 50 ml of dimethylformamide was dissolved 2.93 g of the compound No.1 obtained in Reference Example 7, to which was added 0.29 g of 60% sodium hydride. The mixture was stirred for 30 minutes at room temperature, to which was added 4.33 ml of 1,2-dibromoethane, then the mixture was stirred for further 5 hours. The reaction mixture was poured into 150 ml of pure water, which was subjected to extraction with 150 ml of ethyl acetate. The organic layer was washed twice with 150 ml each portion of a saturated aqueous saline solution, which was dried over sodium sulfate, followed by distilling off the solvent under reduced pressure to leave an oily residue. The oily residue was subjected to a silica gel (150 g) column chromatography, eluting with dichloromethane - ethyl acetate (4:1), to afford 1.05 g of the title compound as a colorless oily product.

Elemental Analysis for $C_{21}H_{22}BrNO_2$:			
Calcd.:	C, 63.01;	H, 5.54;	N, 3.50
Found :	C, 63.07;	H, 5.62;	N, 3.53

Reference Example 9

Using the compound obtained in Reference Example 7, substantially the same procedure as in Reference Example 8 was followed to give the compound shown in Table 38.

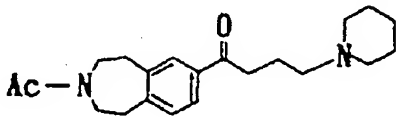
[Table 38]



Compound No.	X	k	m	n	R^2	Y	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
1	NCH_2Ph	2	2	3	Ph	Br	oil	$C_{27}H_{28}BrNO$	70.13 (70.02	6.10 6.13	3.03 3.02)

Working Example 1

1-(3-Acetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-(piperidin-1-yl)-1-butanone

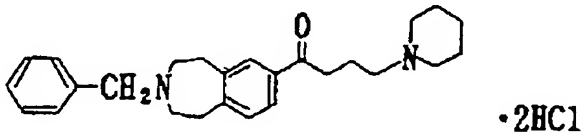


To a solution of 2.64 g of the compound obtained in Reference Example 1 in 50 ml of toluene, were added 1.50 g of piperidine and 20 mg of KI. The mixture was stirred for 12 hours under reflux. The reaction mixture was cooled, to which was then added 50 ml of pure water. The organic layer was separated, from which the solvent was distilled off to leave an oily residue. The residue was purified by means of alumina chromatography (developing solvent; ethyl acetate) to afford 2.15 g of the title compound as colorless powder.

Elemental Analysis for $C_{21}H_{30}N_2O_2$:			
Calcd.:	C, 73.65;	H, 8.83;	N, 8.18
Found :	C, 73.60;	H, 8.74;	N, 8.09

Working Example 2

1-[3-(Phenylmethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-4-(piperidin-1-yl)-1-butanone dihydrochloride



To 2.10 g of the compound obtained in Working Example 1 was added 21 ml of conc. hydrochloric acid, and the mixture was heated for 16 hours under reflux. Excess volume of the conc. hydrochloric acid was distilled off under reduced pressure. To the residue was added 50 ml of water, and the mixture was washed with 50 ml of dichloromethane. The aqueous layer was made basic with an aqueous solution of sodium hydroxide, which was subjected to extraction with dichloromethane. The extract solution was dried over anhydrous sodium sulfate, then the solvent was distilled off to leave 1.80 g of an oily substance.

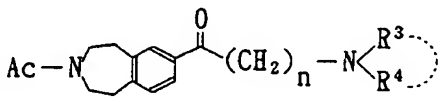
To a suspension of 1.80 g of the above-mentioned oily substance and 1.30 g of potassium carbonate in 20 ml of ethanol was added dropwise a solution of 0.97 g of benzyl bromide in 5 ml of ethanol. The mixture was stirred for 4 hours at room temperature. The solvent was distilled off under reduced pressure. To the residue was added 30 ml of water, and the mixture was subjected to extraction with dichloromethane. The extract solution was dried over anhydrous sodium sulfate, followed by distilling off the solvent to give 1.37 g of the free form of the title compound as colorless powder, m.p.90-92 °C. 1.0 g of the thus obtained free compound was dissolved in methanol, to which was added 1.5 ml of 4N-methanolic hydrochloride. The solvent was distilled off under reduced pressure to leave a solid substance, which was recrystallized from methanol - ethyl acetate to afford 0.93 g of the title compound as colorless crystals, m.p.210-215 °C (decomp.)

Elemental Analysis for $C_{26}H_{34}N_2O \cdot 2HCl$:			
Calcd.:	C, 67.38;	H, 7.83;	N, 6.04
Found :	C, 67.12;	H, 7.81;	N, 6.00

Working Example 3

Using the compound obtained in Reference Example 2, the procedure of Working Example 1 was followed to give compounds shown in Table 39.

[Table 39]

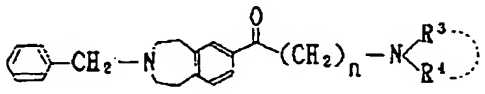


Compound No.	n	$N\langle^{R^3}_{R^4}$	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
1	2	N⟨ ⟩	113−115	$C_{19}H_{26}N_2O_2$	65.04	7.76	7.98
				·HCl	(64.91	7.74	7.96)
2	2	N⟨ ⟩	181−182	$C_{20}H_{28}N_2O_2$	65.83	8.01	7.68
				·HCl	(65.63	7.94	7.73)
3	2	N⟨ ⟩O	99−103	$C_{19}H_{26}N_2O_3$	62.20	7.42	7.64
				·HCl	(61.95	7.44	7.58)
4	2	N⟨ ⟩N-CH_2Ph	170−175	$C_{26}H_{33}N_3O_2$	59.09	7.44	7.95
				·2HCl·$2H_2O$	(58.83	7.34	7.78)
5	2	N⟨ ⟩-CH_2Ph	amorphous powder	$C_{27}H_{34}N_2O_2$	66.04	8.00	5.70
				·HCl·$2H_2O$	(65.70	8.05	5.66)

Working Example 4

Using the compound obtained in Working Example 3, the procedure of Working Example 2 was followed to give the compound shown in Table 40.

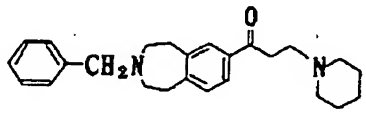
[Table 40]



Compound No.	n	$N\langle^{R^3}_{R^4}$	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
1	2	N⟨ ⟩	163−165	$C_{25}H_{32}N_2O$	66.81	7.62	6.23
				·2HCl	(66.83	7.54	6.24)

Working Example 5

1-[3-(Phenylmethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-3-(piperidin-1-yl)-1-propanone dihydrochloride



·2HCl

To a solution of 1.40 g of the compound obtained in Reference Example 3, 1.22 g of piperidine hydrochloride, 1.5 g of paraformaldehyde in 50 ml of ethanol was added 0.7 ml of conc. hydrochloride, and the mixture was stirred for 24 hours under reflux. The solvent was distilled off. To the residue were added 50 ml of ethyl acetate and 50 ml of pure water. The aqueous layer was separated, whose pH was adjusted to not lower than 10, followed by extraction with 50 ml of ethyl acetate. The extract solution was dried over anhydrous sodium sulfate, from which the solvent was distilled off to leave 2.15 g of an oily residue.

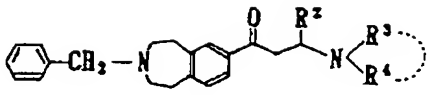
The residue was purified by means of alumina chromatography (developing solvent; dichloromethane - ethyl acetate = 9:1) to give 1.4 g of an oily substance. The oily substance was dissolved in 15 ml of methanol, to which was added 2.0 ml of 4N methanolic hydrochloric acid. The solvent was distilled off, and the crystalline residue was recrystallized from ethanol - ethyl acetate to afford 1.05 g of the title compound as colorless crystals, m.p.163-165 °C.

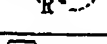
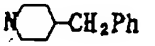
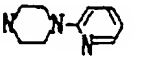
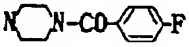
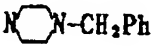
Elemental Analysis for $C_{25}H_{32}N_2O \cdot 2HCl$:			
Calcd.:	C, 66.81;	H, 7.62;	N, 6.23
Found :	C, 66.65;	H, 7.64;	N, 6.17

Working Example 6

Using the compound obtained in Reference Example 3, the procedure of Working Example 5 was followed to give compounds shown in Table 41.

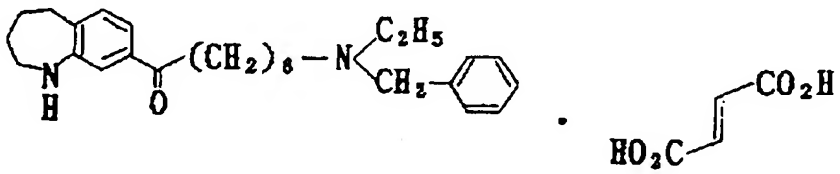
[Table 41]



Compound No.	R^2		m.p. (℃)	Molecular Formula	Elemental Analysis Calcd.(Found) C	H	N
1	H		Amorphous powder	$C_{31}H_{37}N_3O$ ·3HCl	64.53 (64.69	6.99 7.17	7.28 6.99)
2	H		183-186	$C_{32}H_{38}N_2O$ ·2HCl·2H_2O	66.77 (66.96	7.70 7.50	4.87 4.70)
3	H		183-188 (decomp.)	$C_{29}H_{34}N_4O$ ·3HCl·2H_2O	58.05 (57.84	6.89 6.92	9.34 9.26)
4	H		Amorphous powder	$C_{31}H_{34}FN_3O_2$ ·2HCl·H_2O	63.05 (63.23	6.49 6.73	7.12 6.84)
5	H		100-102	$C_{31}H_{37}N_3O$	79.62 (79.55	7.97 7.99	8.99 8.84)

Working Example 7

7-[N-ethyl-N-(phenylmethyl)amino]-1-(2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)-1-heptanone fumarate



(1) A mixture of 1.7 g of ethyl β-(1-acetyl-2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)-β-oxopropionate, 2.6 g of 1,5-dibromopentane, 0.93 g of potassium carbonate and 50 ml of acetone was heated for 16 hours under reflux. The reaction mixture was left standing for cooling, then the resulting solid matter was filtered off. From the filtrate was distilled off the solvent. The residue was purified by means of column chromatography (developing solvent; dichloromethane - ethyl acetate = 10:1(V/V)) to afford 1.8 g of ethyl β-(1-acetyl-2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)-α-(5-bromopentyl)-β-oxopropionate as a viscous oily substance.

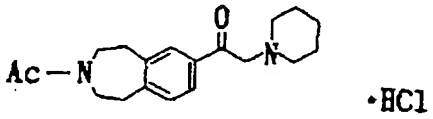
Elemental Analysis for $C_{22}H_{30}BrNO_4$:			
Calcd.:	C, 58.41;	H, 6.68;	N, 3.10
Found :	C, 58.26;	H, 6.63;	N, 3.04

(2) A solution of 0.5 g of the compound obtained in (1) and 0.3 g of N-ethylbenzylamine in 10 ml of toluene was heated for 24 hours under reflux. The reaction mixture was left standing for cooling, then the resulting solid matter was filtered off. From the filtrate was distilled off the solvent. To the residue was added 30 ml of conc. hydrochloric acid. The mixture was heated for 24 hours under reflux, then excess volume of conc. hydrochloric acid was distilled off under reduced pressure. To the residue was added a 5% aqueous solution of sodium hydroxide, which was subjected to extraction with dichloromethane. The extract solution was dried over anhydrous sodium sulfate, from which the solvent was distilled off. The residue was purified by means of column chromatography (developing solvent; ethyl acetate - methanol = 20:1(V/v)) to give 55 mg of a colorless oily product, which was processed with 16 mg(one equivalent) of fumaric acid to afford 60 mg of the title compound as an amorphous powder.

Elemental Analysis for $C_{26}H_{36}N_2O \cdot C_4H_4O_4$:			
Calcd.:	C, 70.84;	H, 7.93;	N, 5.51
Found :	C, 70.59;	H, 8.04;	N, 5.47

Working Example 8

1-(3-Acetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-2-(piperidin-1-yl)-1-ethanone hydrochloride

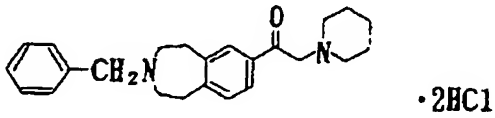


In 10 ml of dichloromethane was dissolved 1.50 g of 1-(3-acetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-2-chloro-1-ethanone obtained in Reference Example 2. To the solution was added 1.7 ml of piperidine, and the mixture was stirred for one hour at room temperature. The reaction mixture was poured into an aqueous solution of potassium carbonate, which was subjected to extraction with dichloromethane. The extract was dried over anhydrous sodium sulfate, from which was distilled off the solvent to leave an oily residue. To the residue was dissolved in 5 ml of methanol, to which was added 1.7 ml of 4N methanolic hydrochloric acid. Then the solvent was distilled off to leave 1.50 g of the title compound as colorless powder.

Elemental Analysis for $C_{19}H_{26}N_2O_2 \cdot HCl$:			
Calcd.:	C, 65.04;	H, 7.76;	N, 7.98
Found :	C, 64.92;	H, 7.81;	N, 7.87

Working Example 9

1-[3-(Phenylmethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-2-(piperidin-1-yl)-1-ethanone dihydrochloride



To 1.40 g of the compound obtained in Working Example 8 was added 20 ml of conc. hydrochloric acid. The mixture was stirred for 13 hours under reflux. The reaction mixture was cooled to 25 °C, to which was added 50 ml of pure water. The mixture was washed with 50 ml of dichloromethane. The aqueous layer was made basic with an aqueous solution of sodium hdyroxide, which was subjected to extraction with 50

ml of dichloromethane. The extract was dried over anhydrous sodium sulfate, from which was distilled off the solvent to leave 1.15 g of an oily product.

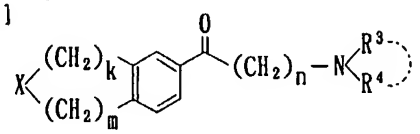
To a suspension of 0.50 g of the above-mentioned oily product and 0.31 g of potassium carbonate in 10 ml of ethanol was added dropwise a solution of 0.30 g of benzyl bromide in 5 ml of ethanol, and the mixture was stirred for 16 hours at room temperature. The solvent was distilled off. To the residue were added 20 ml of dichloromethane and 20 ml of pure water. The organic layer was separated, dried over anhydrous sodium sulfate, followed by distilling off the solvent. The residue was dissolved in 10 ml of methanol, to which was added 1.1 ml of 4N methanolic hydrochloric acid. The solvent was then distilled off to leave a solid matter. Recrystallization from methanol - ethyl acetate afforded 0.2 g of the title compound as colorless crystals, m.p.236-239 • C (decomp.).

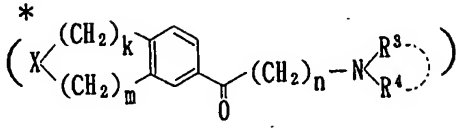
Elemental Analysis for $C_{24}H_{30}N_2O \cdot 2HCl$:			
Calcd.:	C, 66.20;	H, 7.41;	N, 6.43
Found :	C, 66.11;	H, 7.39;	N, 6.38

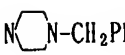
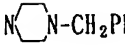
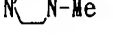
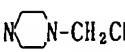
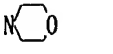
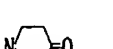
Working Example 10

Using the compounds obtained in Reference Example 1 or Reference Example 5, the procedure of Working Example 1 was followed to give compounds shown in Table 42, Table 43, Table 44 and Table 45.

[Table 42]





Compound No.	X	k	m	n	N(R3)(R4)	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd.(Found) C	H	N
1	NAc	0	4	2		163-167	$C_{26}H_{33}N_3O_2$ ·2HCl	63.41 (63.24	7.16 7.05	8.53 8.48)
2	NCO_2Et	0	4	2		160-163	$C_{27}H_{35}N_3O_3$ ·2HCl·1/2H_2O	61.01 (61.06	7.21 7.33	7.91 7.89)
3	NCH_2Ph	2	2	2		198-202	$C_{25}H_{33}N_3O$ ·3HCl·2H_2O	55.92 (56.29	7.51 7.55	7.83 7.40)
4	NCH_2Ph	2	2	2		165-168	$C_{26}H_{35}N_3O_2$ ·3HCl·3/2H_2O	55.97 (55.69	7.41 7.55	7.53 7.26)
5	NCH_2Ph	2	2	2		176-179	$C_{24}H_{30}N_2O_2$ ·2HCl·1/2H_2O	62.61 (62.33	7.21 7.38	6.08 5.83)
6	NCH_2Ph	2	2	2		155-157	$C_{25}H_{30}N_2O_2$ ·2HCl·2H_2O	60.12 (60.14	7.26 7.53	5.61 5.39)
7	NCH_2Ph	2	2	2		181-184	$C_{33}H_{38}N_4O_2$ ·1/2H_2O	74.55 (74.45	7.39 7.39	10.12 10.12)
8	NCH_2Ph	2	2	2		198-203	$C_{29}H_{32}N_2O$ ·2HCl·H_2O	67.57 (67.85	7.04 7.05	5.43 5.15)
9	NCH_2Ph	2	2	2		amorphous powder	$C_{26}H_{33}N_3O_2$ ·2HCl·2H_2O	59.09 (59.24	7.44 7.21	7.95 7.99)

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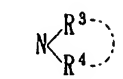
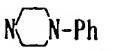
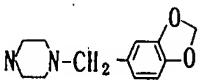
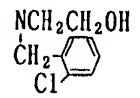
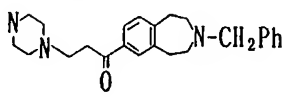
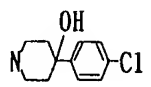
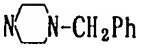
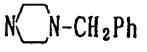
[Table 43]

Compound No.	X	k	m	n		m.p. (℃)	Molecular Formula	Elemental Analysis Calcd.(Found) C	H	N
10	NCH_2Ph	2	2	2		168-171	$C_{30}H_{35}N_3O$	62.02	6.94	7.23
							$\cdot 3HCl \cdot H_2O$	(62.18	6.92	7.20)
11	NCH_2Ph	2	2	2		174-177	$C_{32}H_{37}N_3O_3$	56.93	6.87	6.22
							$\cdot 3HCl \cdot 3H_2O$	(57.17	6.73	5.93)
12	NCH_2Ph	2	2	2		amorphous powder	$C_{29}H_{33}ClN_2O_2$	59.44	6.71	4.78
							$\cdot 2HCl \cdot 2H_2O$	(59.76	6.69	4.41)
13	NCH_2Ph	2	2	2		137-139	$C_{44}H_{52}N_4O_2$	77.96	7.88	8.26
							$\cdot 1/2H_2O$	(77.98	7.98	8.40)
14	NCH_2Ph	2	2	2		243-248 (decomp.)	$C_{31}H_{35}ClN_2O_2$	64.64	6.47	4.86
							$\cdot 2HCl$	(64.49	6.56	4.77)
15	NCH_2Ph	2	2	1		amorphous powder	$C_{30}H_{35}N_3O$	59.26	7.13	6.91
							$\cdot 3HCl \cdot 5/2H_2O$	(59.39	7.23	6.60)
16	NCH_2Ph	2	2	5		182-185	$C_{34}H_{43}N_3O$	65.96	7.49	6.79
							$\cdot 3HCl$	(65.92	7.58	6.68)
17	NAc	2	2	3		122-125	$C_{27}H_{35}N_3O_2$	74.79	8.14	9.69
								(74.58	8.16	9.63)

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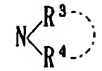
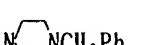
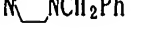
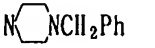
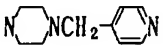
[Table 44]

Compound No.	X	k	m	n		m.p. (℃)	Molecular Formula	Elemental Analysis Calcd.(Found) C	H	N
*18	NCHO	2	0	2		194-196	$C_{23}H_{27}N_3O_2$	60.13	6.58	9.15
							·2HCl·1/2H_2O	(60.16	6.53	9.09)
19	NCHO	1	3	2		213-215 (decomp.)	$C_{25}H_{31}N_3O_2$ ·2HCl·1/2H_2O	61.60 (61.77	7.03 6.99	8.62 8.50)
*20	NCHO	2	0	2		82- 84	$C_{23}H_{27}N_3O_2$	73.18	7.21	11.13
								(72.91	7.32	11.11)
21	NCH_2Ph	2	2	2		186-189	$C_{30}H_{36}N_4O$	53.90	6.94	8.38
							·4HCl·3H_2O	(53.71	7.06	8.65)
22	NCHO	2	2	2		106-108	$C_{25}H_{31}N_3O_2$	74.04	7.70	10.36
								(73.99	7.70	10.39)
23	NAc	2	2	4		191-194	$C_{28}H_{37}N_3O_2$	58.53	7.89	7.31
							·2HCl·3H_2O	(58.71	7.63	7.18)
24	NCH_2Ph	2	2	2		168-172	$C_{25}H_{31}N_3O_2$	58.36	7.25	8.17
							·2HCl·2H_2O	(58.60	7.17	8.15)
25	NCH_2Ph	2	2	2		138-139	$C_{34}H_{36}N_2O$	69.38	7.02	4.76
							·2HCl·3/2H_2O	(69.65	7.06	4.69)

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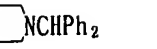
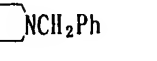
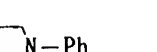
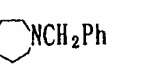
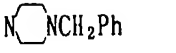
[Table 45]

Compound No.	X	k	m	n		m.p. (℃)	Molecular Formula	Elemental Analysis Calcd.(Found) C	H	N
26	NCH_2Ph	2	2	2		140-142	$C_{37}H_{41}N_3O$	81.73	7.60	7.73
								(81.53	7.62	7.62)
27	NCO_2CH_3	2	2	2		98-101	$C_{26}H_{33}N_3O_3$	71.70	7.64	9.65
								(71.83	7.69	9.68)
*28	NCHO	2	0	2		236-238 (decomp.)	$C_{22}H_{25}N_3O_2$ ·2HCl·5/2H_2O	54.89	6.70	8.73
								(54.70	6.52	9.01)
29	NCH_2Ph	2	2	2		amorphous powder	$C_{32}H_{39}N_3O$ ·3HCl·H_2O	63.10	7.28	6.90
								(62.98	7.10	7.03)
*30	NCHO	3	0	2		218-221 (decomp.)	$C_{24}H_{29}N_3O_2$ ·2HCl·1/2H_2O	60.89	6.81	8.88
								(61.11	6.64	9.11)
*31	NCHO	2	0	2		oil	$C_{24}H_{29}N_3O_2$	73.63	7.47	10.73
								(73.81	7.50	10.61)
32	NCHO	0	3	2		202-207 (decomp.)	$C_{24}H_{29}N_3O_2$ ·2HCl·1/2H_2O	60.89	6.81	8.88
								(61.01	6.75	8.96)
33	NCHO	0	5	2		187-191 (decomp.)	$C_{26}H_{33}N_3O_2$ ·2HCl·H_2O	61.17	7.31	8.23
								(60.87	7.28	8.23)
34	NAc	0	5	2		185-190 (decomp.)	$C_{27}H_{35}N_3O_2$ ·2HCl·H_2O	61.83	7.49	8.01
								(61.89	7.37	8.24)

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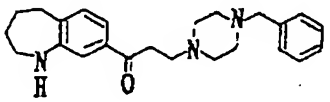
Working Example 11

3-[4-(Phenylmethyl)piperazin-1-yl]-1-(2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)-1-propanone trihydrochloride



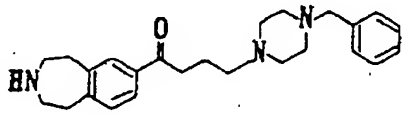
· 3HCl

In 100 ml of 6N hydrochloric acid was dissolved 2.0 g of the compound No.2 in Working Example 10. The solution was heated for 16 hours under reflux. Hydrochloric acid was distilled off under reduced pressure. The residue was dissolved in water, which was neutralized with a 5% aqueous solution of sodium hydroxide, followed by extraction with dichloromethane. The extract solution was dried over anhydrous sodium sulfate, from which was distilled off the solvent. The residue was purified by means of column chromatography (developing solvent; ethyl acetate - methanol = 40:1 (v/v)) to give 1.2 g of the starting compound (free base) and 0.3 g of the title compound (free base). The title compound (free base) (0.3 g) was treated with triequivalent hydrochloric acid to afford 0.35 g of the title compound (trihydrochloride) as colorless powder, m.p.145-149 °C.

Elemental Analysis for $C_{24}H_{31}N_3O \cdot 3HCl$:			
Calcd.:	C, 59.20;	H, 7.04;	N, 8.63
Found :	C, 59.04;	H, 7.20;	N, 8.53

Working Example 12

1-(2,3,4,5-Tetrahydro-1H-3-benzazepin-7-yl)-4-[4-(phenylmethyl)piperazin-1-yl)-1-butanone trihydrochloride



· 3HCl

To 2.17 g of 1-(3-acetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-(phenylmethyl)piperazin-1-yl]-1-butanone, i.e. Compound No. 17 in Working Example 10, was added 50 ml of conc. hydrochloric acid. The mixture was heated for 24 hours under reflux. Excess amount of conc. hydrochloric acid was distilled off under reduced pressure. To the residue was added 50 ml of water. The mixture was washed with 50 ml of dichloromethane. The aqueous layer was made basic with an aqueous solution of sodium hydroxide, which was subjected to extraction with dichloromethane. The extract solution was dried over anhydrous sodium sulfate. The solvent was distilled off to give 2.0 g of an oily product.

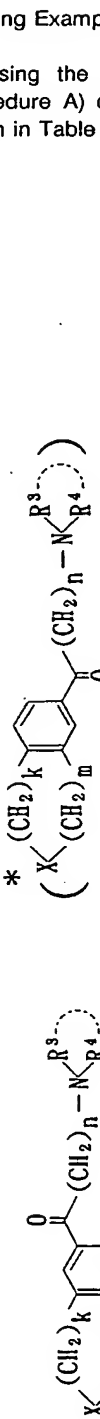
The above-mentioned oily product was dissolved in methanol, to which was added 4.5 ml of 4N-methanolic hydrochloric acid. The solvent was distilled off to leave colorless crystals. The crystals were suspended in 50 ml of ethyl acetate - ether (1:1), followed by collecting the crystals by filtration to give 2.1 g of the title compound as colorless crystals, m.p.201-204 °C.

Elemental Analysis for $C_{25}H_{33}N_3O \cdot 3HCl \cdot H_2O$:			
Calcd.:	C, 57.86;	H, 7.38;	N, 8.10
Found :	C, 57.46;	H, 7.36;	N, 8.28

Working Example 13

Using the compound obtained in Working Example 10, the procedure of Working Example 11 (procedure A) or the procedure of Working Example 12 (procedure B) was followed to give compounds shown in Table 46.

[Table 46]



Compound No.	Method	X	k	m	n		m.p. (°C)	Molecular Formula	Elemental Analysis Calcd.(Found) C	H	N
1	A	NH	2	2	2	N◯NCH$_2$Ph	170-173	$C_{24}H_{31}N_3O$ ·3HCl·2H$_2$O	55.12 (54.96)	7.32 (7.40)	8.04 (8.14)
* 2	A	NH	2	0	2	N◯NCH$_2$Ph	196 (decomp.)	$C_{22}H_{27}N_3O$ ·3HCl·1/2H$_2$O	56.47 (56.61)	6.68 (6.55)	8.98 (9.11)
3	A	NH	1	3	2	N◯NCH$_2$Ph	188-191 (decomp.)	$C_{24}H_{31}N_3O$ ·3HCl·1/2H$_2$O	58.13 (58.11)	7.11 (7.31)	8.44 (8.44)
4	B	NH	2	2	4	N◯NCH$_2$Ph	228-233	$C_{26}H_{35}N_3O$ ·3HCl·2H$_2$O	56.68 (56.98)	7.68 (7.42)	7.63 (7.82)
5	A	NCH$_2$Ph	2	2	2	N◯NH	187-190	$C_{24}H_{31}N_3O$ ·3HCl·5/2H$_2$O	54.19 (54.41)	7.39 (7.51)	7.90 (7.65)
* 6	A	NH	2	0	2	N◯NCH$_2$Ph	97- 99	$C_{22}H_{27}N_3O$	75.61 (75.26)	7.79 (7.74)	12.02 (11.99)
* 7	A	NH	2	0	2	N◯N−Ph	140-142 (decomp.)	$C_{21}H_{25}N_3O$ ·3HCl·H$_2$O	54.50 (54.54)	6.53 (6.54)	9.08 (8.82)
* 8	A	NH	3	0	2	N◯NCH$_2$Ph	174-176 (decomp.)	$C_{23}H_{29}N_3O$ ·3HCl·H$_2$O	56.27 (56.52)	6.98 (6.82)	8.56 (8.58)
* 9	A	NH	2	0	2	N◯NCH$_2$Ph	159-163	$C_{23}H_{29}N_3O$ ·3HCl·H$_2$O	56.27 (55.97)	6.98 (7.05)	8.56 (8.41)
10	A	NH	0	3	2	N◯NCH$_2$Ph	205-211 (decomp.)	$C_{23}H_{29}N_3O$ ·3HCl	58.42 (58.19)	6.82 (6.82)	8.89 (8.70)
11	A	NH	0	5	2	N◯NCH$_2$Ph	194-196 (decomp.)	$C_{25}H_{33}N_3O$ ·3HCl·1/2H$_2$O	58.88 (59.15)	7.31 (7.45)	8.24 (8.30)

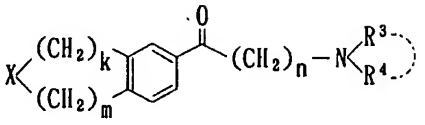
Working Example 14

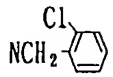
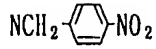
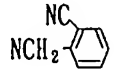
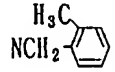
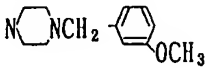
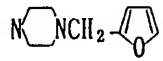
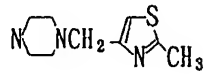
By using the compound obtained in Working Example 13, the procedure of Working Example 1 was followed to give compounds shown in Tables 47 - 51.

[Table 47]

Compound No.	X	k	m	n	R³–N(R⁴)	m.p. (°C)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
* 1	NCH_2Ph	2	0	2		172-174	$C_{29}H_{33}N_3O$ ·3HCl·3H₂O	57.76 (57.75	7.02 6.75	6.97 7.15)
2	NCH_2Ph	1	3	2		221-223 (decomp.)	$C_{31}H_{37}N_3O$ ·3HCl·1/2H₂O	63.53 (63.71	7.05 6.93	7.17 7.17)
3	NCH_2Ph	2	2	4		234-238	$C_{33}H_{41}N_3O$ ·3HCl·3/2H₂O	62.70 (62.72	7.49 7.55	6.65 6.72)
4		2	2	2		amorphous powder	$C_{31}H_{38}ClN_3O$ ·3HCl·3/2H₂O	58.31 (58.45	6.63 6.91	6.58 6.58)
5	NC_2H_5	2	2	2		amorphous powder	$C_{28}H_{35}N_3O$ ·3HCl·5/2H₂O	55.76 (55.88	7.74 7.94	7.50 7.60)
6	NCH_2Ph	2	2	2		168-171	$C_{31}H_{36}ClN_3O$ ·3HCl·3/2H₂O	58.31 (58.32	6.63 6.76	6.58 6.33)
7	NCH_2Ph	2	2	2		176-180	$C_{31}H_{36}ClN_3O$ ·3HCl·3/2H₂O	58.31 (58.21	6.63 6.99	6.58 6.35)
8	NCH_2Ph	2	2	2		173-176	$C_{31}H_{36}ClN_3O$ ·3HCl·5/2H₂O	56.71 (56.59	6.76 6.54	6.40 6.13)
* 9	NCH_2Ph	2	0	2		202-204 (decomp.)	$C_{28}H_{31}N_3O$ ·2HCl	67.46 (67.19	6.67 6.70	8.43 8.36)

[Table 48]



Compound No.	X	k	m	n		m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
10		2	2	2		130-132	$C_{31}H_{36}ClN_3O$	74.16	7.23	8.37
								(73.86	7.25	8.21)
11		2	2	2		amorphous powder	$C_{31}H_{36}ClN_3O$ ·3HCl·9/2H_2O	53.76	6.99	6.07
								(54.01	6.65	5.92)
12		2	2	2		170-172	$C_{31}H_{36}N_4O_3$	55.82	6.65	8.40
							·3HCl·5/2H_2O	(55.76	6.68	8.34)
13		2	2	2		161-163	$C_{32}H_{36}N_4O$	60.24	6.79	8.78
							·3HCl·2H_2O	(59.81	6.99	8.72)
14		2	2	2		amorphous powder	$C_{32}H_{38}N_3O$	61.29	7.39	6.70
							·3HCl·2H_2O	(61.41	7.50	6.64)
15	NCH_2Ph	2	2	2		amorphous powder	$C_{32}H_{38}N_3O_2$	58.94	7.26	6.44
							·3HCl·5/2H_2O	(58.96	7.10	6.42)
16	NCH_2Ph	2	2	2		172-175	$C_{32}H_{38}N_3O$	60.42	7.45	6.61
							·3HCl·5/2H_2O	(60.30	7.32	6.60)
17	NCH_2Ph	2	2	2		110-113	$C_{29}H_{35}N_3O_2$	76.12	7.71	9.18
								(76.01	7.73	9.10)
18	NCH_2Ph	2	2	2		amorphous powder	$C_{29}H_{36}N_4OS$ ·3HCl·7/2H_2O	52.69	7.01	8.47
								(52.74	7.10	8.69)

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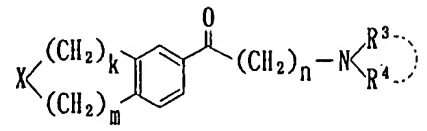
[Table 49]



Compound No.	X	k	m	n	N(R3)(R4)	m.p. (°C)	Molecular Formula	Elemental Analysis Calcd.(Found) C	H	N
19	NCH_2-(4-CN)	2	2	2	N-NCH_2Ph	202-205 (decomp.)	$C_{32}H_{36}N_4O$ ·3HCl·H_2O	61.99 (61.80	6.66 6.78	9.04 9.05)
20	NCH_2-(2-F)	2	2	2	N-NCH_2Ph	165-168	$C_{31}H_{36}FN_3O$ ·3HCl·$2H_2O$	59.00 (58.76	6.87 6.96	6.66 6.59)
21	NCH_2-(2-CH_3O)	2	2	2	N-NCH_2Ph	amorphous powder	$C_{32}H_{38}N_3O_2$ ·3HCl·3/$2H_2O$	60.62 (60.89	7.15 7.24	6.63 6.46)
22	NCH_2-(2,3-OCH_3,OCH_3)	2	2	2	N-NCH_2Ph	171-174 (decomp.)	$C_{33}H_{41}N_3O_3$ ·3HCl·5/$2H_2O$	58.11 (58.32	7.24 7.50	6.16 6.16)
23	NCH_2-(4-CH_3)	2	2	2	N-NCH_2Ph	198-201 (decomp.)	$C_{32}H_{39}N_3O$ ·3HCl·H_2O	63.10 (63.33	7.28 7.33	6.90 6.84)
24	NCH_2-(4-F)	2	2	2	N-NCH_2Ph	178-180	$C_{32}H_{36}FN_3O$ ·3HCl·3/$2H_2O$	59.86 (59.93	6.81 6.87	6.76 6.57)
25	NCH_2-(2-CH_3)	2	2	2	N-NCH_2Ph	178-181 (decomp.)	$C_{32}H_{39}N_3O$ ·3HCl·3/$2H_2O$	62.18 (62.15	7.34 7.46	6.80 6.72)
26	NCH_2-(2-F)	2	2	2	N-NCH_2Ph	170-172	$C_{31}H_{36}FN_3O$ ·3HCl·5/$2H_2O$	58.17 (58.45	6.93 7.02	6.56 6.50)
27	NCH_2-(3-OCH_3)	2	2	2	N-NCH_2Ph	173-176	$C_{32}H_{38}N_3O_2$ ·3HCl·$2H_2O$	59.77 (60.10	7.21 7.44	6.53 6.56)

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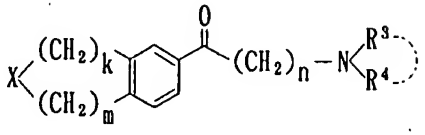
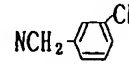
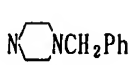
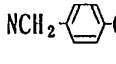
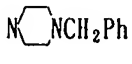
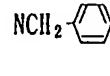
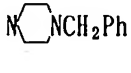
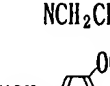
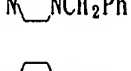
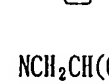
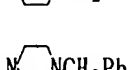
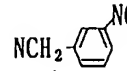
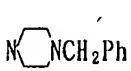
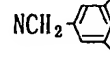
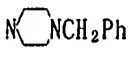
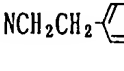
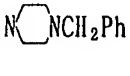
[Table 50]



Compound No.	X	k	m	n	N(R3)(R4)	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
28		2	2	2		177-180	$C_{32}H_{36}N_4O$ ·3HCl·3/2H_2O	61.10 (60.94	6.73 6.94	8.91 8.85)
29		2	2	2		181-184	$C_{32}H_{39}N_3O_2$ ·3HCl·3/2H_2O	60.62 (60.56	7.15 7.33	6.63 6.58)
30		2	2	2		amorphous powder	$C_{31}H_{37}N_3O_2$ ·3HCl·5/2H_2O	58.35 (58.45	7.11 7.13	6.59 6.56)
31		2	2	2		217-221 (decomp.)	$C_{32}H_{39}N_3O$ ·3HCl·3/2H_2O	62.18 (62.26	7.34 7.57	6.80 6.88)
32		2	2	2		193-196	$C_{38}H_{43}N_3O_2$ ·3HCl·3/2H_2O	64.27 (64.35	6.95 6.94	5.92 6.10)
33		2	2	2		167-170	$C_{28}H_{39}N_3O$ ·3HCl·3H_2O	56.33 (56.57	8.10 8.25	7.04 7.04)
34		2	2	2		178-181 (decomp.)	$C_{31}H_{36}N_4O_3$ ·3HCl·3/2H_2O	57.37 (57.12	6.52 6.73	8.63 8.47)
35		2	2	2		178-181 (decomp.)	$C_{34}H_{43}N_3O_4$ ·3HCl·H_2O	59.61 (59.53	7.06 7.35	6.13 6.06)
36		2	2	2		178-182 (decomp.)	$C_{34}H_{43}N_3O_3$ ·3HCl·3H_2O	57.91 (58.09	7.43 7.22	5.96 6.00)

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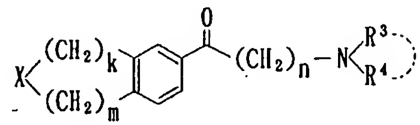
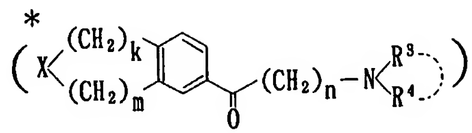
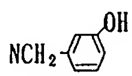
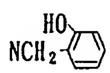
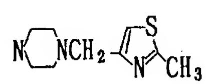
[Table 51]

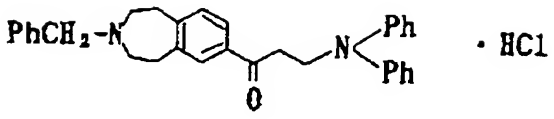




Compound No.	X	k	m	n		m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
37	$NCH_2CH_2CH_3$	2	2	2		177-179	$C_{27}H_{37}N_3O$ ·3HCl·5/2H_2O	56.49 (56.43	7.90 8.12	7.32 7.38)
38	$NCH_2C{\equiv}CH$	2	2	2		168-170	$C_{27}H_{33}N_3O$ ·3HCl·2H_2O	57.81 (57.86	7.19 7.36	7.49 7.40)
39	NCH_2CH_2OH	2	2	2		166-169	$C_{26}H_{35}N_3O_2$ ·3HCl·5/2H_2O	54.22 (54.46	7.52 7.36	7.30 7.03)
40		2	2	2		168-170	$C_{31}H_{37}N_3O_2$ ·3HCl·3/2H_2O	60.05 (59.69	6.99 6.92	6.78 6.80)
41		2	2	2		168-171	$C_{31}H_{37}N_3O_2$ ·3HCl·2H_2O	59.19 (58.78	7.05 6.88	6.68 6.44)
*42	NCH_2Ph	0	2	2		185-187	$C_{29}H_{33}N_3O$ ·2HCl·H_2O	65.65 (66.00	7.03 7.16	7.92 8.00)
43	NCH_2Ph	2	2	2		163-166 (decomp.)	$C_{29}H_{38}N_4OS$ ·4HCl·3/2H_2O	52.65 (52.74	6.55 6.53	8.47 8.44)

Working Example 15

3-Diphenylamino-1-[3-(phenylmethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-propanone hydrochloride

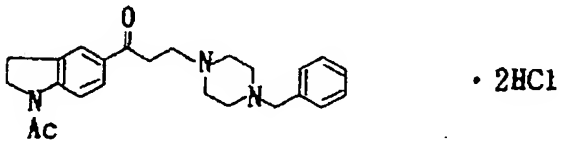


To a solution of 0.98 g of the Compound No. 5 of Reference Example 5 in 30 ml of 1,2-dichloroethane was added 0.63 ml of triethylamine. The mixture was stirred for one hour at room temperature, to which was added 0.56 g of diphenylamine, followed by heating for 72 hours under reflux. The reaction mixture was cooled to room temperature, which was then poured into 50 ml of pure water. To the mixture was added a 1N aqueous solution of sodium hydroxide. The aqueous layer was adjusted to pH not lower than 12, followed by extraction with dichloromethane. The extract solution was dried over anhydrous sodium sulfate, then the solvent was distilled off to leave an oily product. The oily product was purified by means of a silica gel column chromatography (developing solvent: dichloromethane - ethyl acetate = 4:1 (v/v)) to afford 0.30 g of the free base of the title compound. The free base was added to 4N methanolic hydrochloric acid, then the solvent was distilled off. The residue was triturated from diethyl ether - hexane to afford 0.25 g of the title compound as amorphous powder.

Elemental Analysis for $C_{32}H_{32}N_2O \cdot HCl \cdot H_2O$:			
Calcd.:	C, 74.62;	H, 6.85;	N, 5.44
Found :	C, 74.29;	H, 6.91;	N, 5.40

Working Example 16

1-(1-Acetyl-2,3-dihydro-1H-indol-5-yl)-3-[4-(phenylmethyl)piperazin-1-yl]-1-propanone dihydrochloride



To a solution of 0.7 g of the Compound No.6 of Working Example 13 in 40 ml of dichloromethane was added dropwise 0.2 g of acetic anhydride. The mixture was stirred for 2 hours at room temperature. To the reaction mixture was added a saturated aqueous solution of sodium hydrogencarbonate, followed by extraction with dichloromethane. The extract solution was dried over anhdyrous sodium sulfate, then the solvent was distilled off. The residue was crystallized from diethyl ether to give 0.54 g of the free base of the title compound as pale yellow crystals, m.p.107-109 °C.

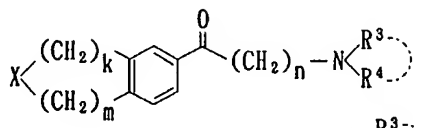
To 0.35 g of the above-mentioned free base was added 4N methanolic hydrochloric acid (2 equivalents), followed by distilling off the solvent to afford 0.35 g of the title compound as crystalline powder, m.p.216-218 °C.

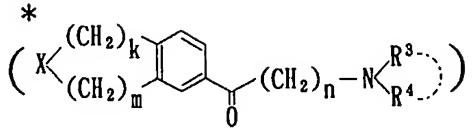
Elemental Analysis for $C_{24}H_{29}N_3O_2 \cdot 2HCl \cdot 2H_2O$:			
Calcd.:	C, 57.60;	H, 7.05;	N, 8.40
Found :	C, 57.47;	H, 6.86;	N, 8.26

Working Example 17

Using the compound of Working Example 13, the procedure of Working Example 16 was followed to afford the compounds shown in Table 52.

[Table 52]





Compound No.	X	k	m	n	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd.(Found) C	H	N
1	NAc	1	3	2	196-200	$C_{26}H_{33}N_3O_2$ ·2HCl·H_2O	61.17 (61.34	7.31 7.33	8.23 8.14)
*2	NAc	2	0	2	236-238 (decomp.)	$C_{23}H_{27}N_3O_2$ ·2HCl·5/2H_2O	54.89 (54.70	6.70 6.52	8.73 9.01)
3	NCOPh	2	2	2	148-151	$C_{31}H_{35}N_3O_2$ ·2HCl·H_2O	65.03 (64.96	6.87 7.05	7.58 7.34)
4		2	2	2	171-173 (decomp.)	$C_{30}H_{34}N_4O_2$ ·3HCl·$3H_2O$	55.77 (55.52	6.71 6.75	8.67 8.43)
5	$NCONHCH_3$	2	2	2	162-164	$C_{26}H_{34}N_4O_2$ ·1/2H_2O	70.40 (70.45	7.95 7.87	12.63 12.49)
*6	NAc	3	0	2	193-196 (decomp.)	$C_{25}H_{31}N_3O_2$ ·2HCl	62.76 (62.47	6.95 7.10	8.78 8.73)

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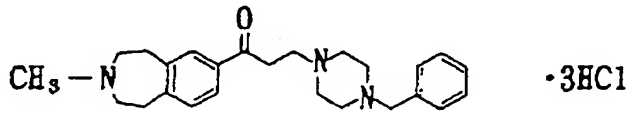
Working Example 18

1-(3-Methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3-[4-(phenylmethyl)piperazin-1-yl]-1-propanone trihydrochloride

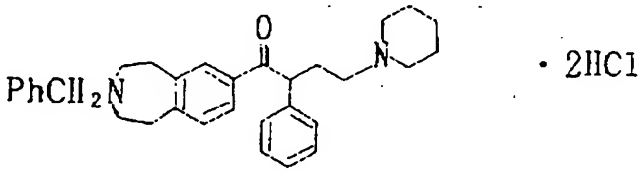


In 30 ml of ethanol was suspended 0.50 g of the compound obtained in Reference Example 6, to which were added 0.55 g of potassium carbonate and 0.42 ml of 1-benzyl piperazine at room temperature. The mixture was stirred for 3 hours, to which were added 50 ml of dichloromethane and 50 ml of pure water. The organic layer was separated and washed with 30 ml of pure water, which was then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to leave 0.2 g of an oily residue. The oily residue was purified by means of an alumina chromatography (developing solvent: dichloromethane - ethyl acetate = 4:1(v/v)) to give 0.17 g an oily residue. To the oily residue was added 3 equivalents of mathanolic hydrochloric acid, then methanol was distilled off to afford 0.2 g of the title compound as amorphous powder.

Elemental Analysis for $C_{25}H_{33}N_3O \cdot 2HCl \cdot 3H_2O$:			
Calcd.:	C, 55.92;	H, 7.51;	N, 7.83
Found :	C, 56.01;	H, 7.78;	N, 7.83

Working Example 19

1-[3-(Phenylmethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-2-phenyl-4-(piperidin-1-yl)-1-butanone dihydrochloride



In 20 ml of dichloromethane was dissolved 0.92 g (2 mmol.) of the compound No.1 obtained in Reference Example 9. To the solution was added 0.99 ml (10 mmol.) of piperidine, and the mixture was stirred for one day at room temperature. The reaction mixture was washed with 20 ml of 1N aqueous solution of sodium hydroxide and 20 ml of pure water, followed by drying over sodium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by means of a silica gel column chromatography [developing solvent: ethyl acetate - methanol (4:1)] to afford 0.53 g of the title compound in the free form as an oily substance.

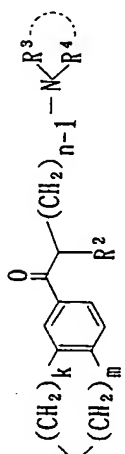
To the oily substance was added 4N-methanolic hydrochloric acid (2 equivalents), then the solvent was distilled off under reduced pressure to give 0.58 g of the title compound as a hydroscopic amorphous powder.

Elemental Analysis for $C_{32}H_{38}N_2O \cdot 2HCl \cdot H_2O$:			
Calcd.:	C, 68.93;	H, 7.59;	N, 5.02
Found :	C, 69.01;	H, 7.55;	N, 5.05

Working Example 20

By substantially the same procedure as in Working Example 19, using the compounds obtained in Reference Example 8 or Reference Example 9, compounds shown in Table 53 were obtained.

[Table 53]



Compound No.	X	k	m	R^2	n	NR^3R^4	m.p. (°C)	Molecular Formula	Elemental Analysis Calcd.(Found) C	H	N
1	NCH_2Ph	2	2	Ph	3	$N(CH_3)_2$	amorphous	$C_{29}H_{34}N_2O$	65.04	7.53	5.23
							powder	$\cdot 2HCl \cdot 2H_2O$	(65.17	7.51	5.20)
2	NCHO	2	2	Ph	3		amorphous	$C_{32}H_{37}N_3O_2$	65.52	7.05	7.16
							powder	$\cdot 2HCl \cdot H_2O$	(65.41	7.01	7.13)

Formulation Example 1

(1)	3-[4-(Phenylmethyl)piperazin-1-yl]-1-[3-(phenylmethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-propanone trihydrochloride (Compound No.1 in [Table 17], Working Example 6)	1 g
(2)	Lactose	197 g
(3)	Corn starch	50 g
(4)	Magnesium stearate	2 g

(1), (2) and 20 g of corn starch were blended and the mixture was granulated with a paste prepared from 15 g of corn starch and 25 ml of water. To this granular product were added 15 g of corn starch and (4), and the resulting composition was compression-molded to provide 2000 tablets each measuring 3 mm in diameter and containing 0.5 mg of (1).

Formulation Example 2

(1)	3-[4-(phenylmethyl)piperazin-1-yl]-1-[3-(phenylmethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-propanone trihydrochloride (Compound No.1 in [Table 17], Working Example 6)	2 g
(2)	Lactose	197 g
(3)	Corn starch	50 g
(4)	Magnesium stearate	2 g

(1), (2) and 20 g of corn starch were blended and the mixture was granulated with a paste prepared from 15 g of corn starch and 25 ml of water. To this granular product were added 15 g of corn starch and (4), and the resulting composition was compression-molded to provide 2000 tablets each measuring 3 mm in diameter and containing 1.0 mg of (1).

Experimental Example 1

The cholinesterase inhibitory activity of the compound of this invention was assayed with (acetyl-[^{3}H])-acetylcholine. More specifically, using the S_1 fraction of a homogenate of male Wistar rat cerebral cortex as the cholinesterase source, (acetyl[^{3}H])-acetylcholine as the substrate and the compound of this invention as the test sample were added. The mixture was incubated for 30 minutes, then the reaction was terminated, to which was added a toluene-based scintillant, then the mixture was shaken. The reaction product [^{3}H]-acetic acid was transferred to the toluene layer, which was subjected to determination of cholinesterase activity by counting with a liquid scintillation counter.

The cholinesterase inhibitory activity of the test compound was expressed in 50% inhibitory concentration (IC_{50}). The cholinesterase activity of physostigmine was also determined by the same procedure. The results are shown in Table 54.

[Table 54]

Compound (Working Example No.)	Acetylcholinesterase inhibitory activity IC_{50} (μM)
3-4	0.119
6-1	0.049
6-5	0.0526
10-18	0.0152
10-19	0.171
10-20	0.0152
10-22	0.0928
10-26	0.0526
10-27	0.169
10-30	0.0599
10-32	0.118
13-1	0.0493
13-3	0.0789
13-8	0.163
14-2	0.0538
14-4	0.147
14-5	0.0188
14-6	0.113
14-10	0.167
14-14	0.0636
14-19	0.0339
14-20	0.0478
14-21	0.0226
14-22	0.0215
14-23	0.0661
14-25	0.0696
14-27	0.133
14-29	0.0257
14-31	0.033
14-33	0.0341
14-36	0.0168
14-40	0.0602
16	0.0251
17-3	0.0825
18	0.0338
Physostigmine	0.220

The results shown in Table 54 indicate that the compound of the present invention has superior cholinesterase inhibitory activity to physostigmine.

Experimental Example 2

Effects of the compound of this invention on monoamine uptake were investigated using [^{3}H]-norepinephirine(NE) and [^{3}H]-serotonin (5-HT). Rats were sacrificed by decapitation. The cerebral cortex and hippocampus were removed and homogenized in 10-15 volumes (W/V) of an ice-cold medium containing 0.32 M sucrose. Crude synaptosomal preparations (P2) were isolated after differential centrifugation at 1000 x g for 10 min and 20,000 x g for 30 min at 4°C. Synaptosomal membranes were suspended in Krebs-Ringer bicarbonate (KRB) solution (116 mM NaCl, 4.8 mM KCl, 1.3 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1.2 mM NaH_2PO_4, 25 mM $NaHCO_3$, 0.1 mM EDTA-2Na, 11.1 mM glucose, 0.11 mM ascorbic acid, 0.01 mM pargyline). Synaptosomal membrane suspension (900 µl) was preincubated with the test compound dissolved in DMSO solution at 37°C for 5 min. The reaction was initiated by addition of 100 µl of [^{3}H]-NE- (11 nM in final concentration) or [^{3}H]-5-HT (10 nM in final concentration). Five minutes later, the reaction was stopped by the addition of 4 ml of ice-cold KRB and the reaction mixture was filtered through Whatman GF/B. Filters were washed twice with 4 ml of KRB and the radioactivity bound was counted with liquid scintillant. Imipramine and desipramine were used as positive control. All compounds were tested at 10^{-8}, 10^{-7}, 10^{-6} and 10^{-5} M. The results are shown in Table 55.

Table 55

Compound (Working Example No.)	Monoamine reuptake inhibitory activity IC_{50}(µM)	
	NE	5-HT
14-1	0. 147	0. 416
14-6	0. 725	0. 0345
14-7	0. 822	0. 0421
14-23	0. 912	0. 0583
14-29	0. 429	0. 0544
14-31	0. 441	0. 0305
14-33	0. 74	0. 0559
14-36	0. 70	0. 0133
14-40	0. 359	0. 0413
Desipramine	0. 15	0. 45
Imipramine	1. 12	0. 063

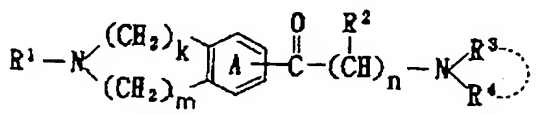
The results shown in Table 55 indicate that the compound of the present invention has superior inhibitory activity of monoamine uptake to reference compounds such as desipramine or imipramine.

[Effects of Invention]

The compound of the present invention has excellent cholinesterase inhibitory activity and monoamine reuptake inhibitory activity and is useful as therapeutic/prophylactic medicament of senile dementia.

Claims

1. A compound of the formula:



[I]

wherein R^1 is H, an optionally substituted hydrocarbon group or an optionally substituted acyl group; ring A is an optionally further substituted benzene ring; n is a whole number of 1 to 10; R^2, R^3 and R^4 are independently H or an optionally substituted hydrocarbon group; R^3 and R^4 may form an optionally substituted heterocyclic group, taken together with the adjacent nitrogen atom; R^2's may be different from one another in the repetition of n; k is a whole number of 0 to 3; and m is a whole number of 1 to

8; provided that when k = 0 and m = 2, n is a whole number of not less than 2, or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1, wherein R^1 is (1) a hydrogen atom, (2) a straight-chain or branched C_{1-11} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl-substituted amino, 5 to 7-membered cyclic amino, C_{1-4} alkyl-carbonylamino, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxy-carbonyl, carboxyl, C_{1-6} alkyl-carbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsulfonyl, C_{1-4} alkylenedioxy and heterocyclic group, (3) a C_{3-7} monocyclic cycloalkyl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkylsubstituted amino, 5 to 7-membered cyclic amino, C_{1-4} alkyl-carbonylamino, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxy-carbonyl, carboxyl, C_{1-6} alkyl-carbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsulfonyl, C_{1-4} alkylenedioxy and heterocyclic group, (4) a C_{8-14} bridge ring saturated hydrocarbon group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono-or di-C_{1-4} alkyl-substituted amino, 5 to 7-membered cyclic amino, C_{1-4} alkyl-carbonylamino, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxy-carbonyl, carboxyl, C_{1-6} alkyl-carbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsulfonyl, C_{1-4} alkylenedioxy and heterocyclic group, (5) a phenyl or naphthyl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C_{1-4} alkyl, halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl-substituted amino, 5 to 7-membered cyclic amino, C_{1-4} alkyl-carbonylamino, C_{7-18} aralkyloxy, aminocarbonyloxy, mono-or di-C_{1-4} alkyl-substituted aminocarbonyloxy, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxy-carbonyl, carboxyl, C_{1-6} alkyl-carbonyl, C_{3-7} cycloalkyl-carbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsulfonyl, C_{3-7} cycloalkylsulfonyl and a phenyl, naphthyl, mono- or di-phenyl-C_{1-3} alkyl, phenoxy, benzoyl, phenoxycarbonyl, benzylcarbonyl, phenyl-C_{1-4} alkyl-carbamoyl, phenylcarbamoyl, phenyl-C_{1-4} alkyl-carbonylamino, benzoylamino, phenyl-C_{1-4} alkylsulfonyl, phenylsulfonyl, phenyl-C_{1-4} alkylsulfinyl, phenyl-C_{1-4} alkylsulfonylamino or phenylsulfonylamino group which may be substituted by 1 to 4 substituents selected from the group consisting of a C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro, C_{1-6} alkyl-carbonyl and benzoyl, (6) a C_{7-18} aralkyl, C_{6-14} aryl-C_{2-12} alkenyl, C_{6-14}aryl-C_{2-12} alkynyl or C_{3-7} cycloalkyl-C_{1-6} alkyl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C_{1-4} alkyl, halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl-substituted amino, 5 to 7-membered cyclic amino, C_{1-4} alkyl-carbonylamino, C_{7-18} aralkyloxy, aminocarbonyloxy, mono-or di-C_{1-4} alkyl-substituted aminocarbonyloxy, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxy-carbonyl, carboxyl, C_{1-6} alkyl-carbonyl, C_{3-7} cycloalkyl-carbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsulfonyl, C_{3-7} cycloalkylsulfonyl and a phenyl, naphthyl, mono- or di-phenyl-C_{1-3} alkyl, phenoxy, benzoyl, phenoxycarbonyl, benzylcarbonyl, phenyl-C_{1-4} alkyl-carbamoyl, phenylcarbamoyl, phenyl-C_{1-4} alkyl-carbonylamino, benzoylamino, phenyl-C_{1-4} alkylsulfonyl, phenylsulfonyl, phenyl-C_{1-4} alkylsulfinyl, phenyl-C_{1-4} alkylsulfonylamino or phenylsulfonylamino group which may be substituted by 1 to 4 substituents selected from the group consisting of a C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro, C_{1-6} alkyl-carbonyl and benzoyl, (7) a C_{1-8} alkyl-carbonyl or C_{6-14} aryl-carbonyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen, amino, mono- or di-C_{1-6} alkyl substituted amino and C_{1-4} alkoxy, (8) a C_{1-7} alkylsulfonyl or C_{6-14} arylsulfonyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen, amino, mono- or di-C_{1-6} alkyl substituted amino and C_{1-4} alkoxy, (9) a C_{1-7} alkylphosphonyl or C_{6-14} arylphosphonyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen, amino, mono- or di-C_{1-6} alkyl substituted amino and C_{1-4} alkoxy, (10) a C_{1-8} alkoxy-carbonyl or C_{7-18} aralkyloxy-carbonyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen, amino, mono- or di-C_{1-6} alkyl substituted amino and C_{1-4} alkoxy, (11) heterocyclic-carbonyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen, amino, mono- or di-C_{1-6} alkyl substituted amino and C_{1-4} alkoxy, (12) carbamoyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen, amino, mono- or di-C_{1-6} alkyl substituted amino and C_{1-4} alkoxy, (13) mono- or di-C_{1-4} alkyl-carbamoyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen, amino, mono- or di-C_{1-6} alkyl substituted amino and C_{1-4} alkoxy, or (14)

formyl; R^2, R^3 and R^4 are independently (1') a hydrogen atom, (2') a straight-chain or branched C_{1-11} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl-substituted amino, 5 to 7-membered cyclic amino, C_{1-4} alkyl-carbonylamino, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxy-carbonyl, carboxyl, C_{1-6} alkyl-carbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsulfonyl, C_{1-4} alkylenedioxy and heterocyclic group, (3') a C_{3-7} monocyclic cycloalkyl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl-substituted amino, 5 to 7-membered cyclic amino, C_{1-4} alkyl-carbonylamino, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxy-carbonyl, carboxyl, C_{1-6} alkyl-carbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsulfonyl, C_{1-4} alkylenedioxy and heterocyclic group, (4') a C_{8-14} bridge ring saturated hydrocarbon group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono-or di-C_{1-4} alkyl-substituted amino, 5 to 7-membered cyclic amino, C_{1-4} alkyl-carbonylamino, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxy-carbonyl, carboxyl, C_{1-6} alkyl-carbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsulfonyl, C_{1-4} alkylenedioxy and heterocyclic group, (5') a phenyl or naphthyl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C_{1-4} alkyl, halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl-substituted amino, 5 to 7-membered cyclic amino, C_{1-4} alkyl-carbonylamino, C_{7-18} aralkyloxy, aminocarbonyloxy, mono-or di-C_{1-4} alkylsubstituted aminocarbonyloxy, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxy-carbonyl, carboxyl, C_{1-6} alkyl-carbonyl, C_{3-7} cycloalkyl-carbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsulfonyl, C_{3-7} cycloalkylsulfonyl and a phenyl, naphthyl, mono- or di-phenyl-C_{1-3} alkyl, phenoxy, benzoyl, phenoxycarbonyl, benzylcarbonyl, phenyl-C_{1-4} alkyl-carbamoyl, phenylcarbamoyl, phenyl-C_{1-4} alkyl-carbonylamino, benzoylamino, phenyl-C_{1-4} alkylsulfonyl, phenylsulfonyl, phenyl-C_{1-4} alkylsulfinyl, phenyl-C_{1-4} alkylsulfonylamino or phenylsulfonylamino group which may be substituted by 1 to 4 substituents selected from the group consisting of a C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro, C_{1-6} alkyl-carbonyl and benzoyl, (6') a C_{7-18} aralkyl, C_{6-14} aryl-C_{2-12} alkenyl, C_{6-14} aryl-C_{2-12} alkynyl or C_{3-7} cycloalkyl-C_{1-6} alkyl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C_{1-4} alkyl, halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4}alkylthio, amino, mono- or di-C_{1-4} alkyl-substituted amino, 5 to 7-membered cyclic amino, C_{1-4} alkyl-carbonylamino, C_{7-18} aralkyloxy, aminocarbonyloxy, mono-or di-C_{1-4} alkyl-substituted aminocarbonyloxy, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxy-carbonyl, carboxyl, C_{1-6} alkyl-carbonyl, C_{3-7} cycloalkyl-carbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsulfonyl, C_{3-7} cycloalkylsulfonyl and a phenyl, naphthyl, mono- or di-phenyl-C_{1-3} alkyl, phenoxy, benzoyl, phenoxycarbonyl, benzylcarbonyl, phenyl-C_{1-4} alkyl-carbamoyl, phenylcarbamoyl, phenyl-C_{1-4} alkyl-carbonylamino, benzoylamino, phenyl-C_{1-4} alkylsulfonyl, phenylsulfonyl, phenyl-C_{1-4} alkylsulfinyl, phenyl-C_{1-4} alkylsulfonylamino or phenylsulfonylamino group which may be substituted by 1 to 4 substituents selected from the group consisting of a C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro, C_{1-6} alkyl-carbonyl and benzoyl, R^3 and R^4 may, taken together with the adjacent nitrogen atom, form a 3- to 13-membered heterocyclic group having, other than carbon atoms and one nitrogen atom, 1 to 3 nitrogen, oxygen and/or sulfur atoms as hetero atoms, which may be substituted by 1 to 5 substituents selected from the group consisting of (1") a straight-chain or branched C_{1-11} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl-substituted amino, 5 to 7-membered cyclic amino, C_{1-4} alkyl-carbonylamino, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxy-carbonyl, carboxyl, C_{1-6} alkyl-carbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsulfonyl, C_{1-4} alkylenedioxy and heterocyclic group, (2") a C_{3-7} monocyclic cycloalkyl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl-substituted amino, 5 to 7-membered cyclic amino, C_{1-4} alkyl-carbonylamino, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxy-carbonyl, carboxyl, C_{1-6} alkyl-carbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsulfonyl, C_{1-4} alkylenedioxy and heterocyclic group, (3") a C_{8-14} bridge ring saturated hydrocarbon group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono-or di-C_{1-4} alkyl-substituted amino, 5 to 7-membered cyclic amino, C_{1-4} alkyl-carbonylamino, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxy-carbonyl, carboxyl, C_{1-6} alkyl-carbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsul-

fonyl, C_{1-4} alkylenedioxy and heterocyclic group, (4") a phenyl or naphthyl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C_{1-4} alkyl, halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl-substituted amino, 5 to 7-membered cyclic amino, C_{1-4} alkyl-carbonylamino, C_{7-18} aralkyloxy, aminocarbonyloxy, mono-or di-C_{1-4} alkyl-substituted aminocarbonyloxy, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxy-carbonyl, carboxyl, C_{1-6} alkyl-carbonyl, C_{3-7} cycloalkyl-carbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsulfonyl, C_{3-7} cycloalkylsulfonyl, C_{1-4} alkylenedioxy and a phenyl, naphthyl, mono- or diphenyl-C_{1-3} alkyl, phenoxy, benzoyl, phenoxycarbonyl, benzylcarbonyl, phenyl-C_{1-4} alkyl-carbamoyl, phenylcarbamoyl, phenyl-C_{1-4} alkyl-carbonylamino, benzoylamino, phenyl-C_{1-4} alkylsulfonyl, phenylsulfonyl, phenyl-C_{1-4} alkylsulfinyl, phenyl-C_{1-4} alkylsulfonylamino or phenylsulfonylamino group which may be substituted by 1 to 4 substituents selected from the group consisting of a C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro, C_{1-6} alkyl-carbonyl and benzoyl, (5") a C_{7-18} aralkyl, C_{6-14} aryl-C_{2-12} alkenyl, C_{6-14} aryl-C_{2-12} alkynyl or C_{3-7} cycloalkyl-C_{1-6} alkyl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C_{1-4} alkyl, halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl-substituted amino, 5 to 7-membered cyclic amino, C_{1-4} alkyl-carbonylamino, C_{7-18} aralkyloxy, aminocarbonyloxy, mono-or di-C_{1-4} alkyl-substituted aminocarbonyloxy, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxy-carbonyl, carboxyl, C_{1-6} alkyl-carbonyl, C_{3-7} cycloalkyl-carbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsulfonyl, C_{3-7} cycloalkylsulfonyl, C_{1-4} alkylenedioxy and a phenyl, naphthyl, mono- or diphenyl-C_{1-3} alkyl, phenoxy, benzoyl, phenoxycarbonyl, benzylcarbonyl, phenyl-C_{1-4} alkyl-carbamoyl, phenylcarbamoyl, phenyl-C_{1-4} alkyl-carbonylamino, benzoylamino, phenyl-C_{1-4} alkylsulfonyl, phenylsulfonyl, phenyl-C_{1-4} alkylsulfinyl, phenyl-C_{1-4} alkylsulfonylamino or phenylsulfonylamino group which may be substituted by 1 to 4 substituents selected from the group consisting of a C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro, C_{1-6} alkyl-carbonyl and benzoyl, (6") halogen atom, (7") nitro group, (8") cyano group, (9") hydroxyl group, (10") C_{1-4} alkoxy group, (11") C_{1-4} alkylthio group, (12") amino group, (13") mono or di C_{1-4} alkylamino group, (14") C_{1-4} alkyl-carbonylamino group, (15") C_{1-4} alkyl-sulfonylamino group, (16") C_{1-4} alkoxycarbonyl group, (17") carboxyl group, (18") formyl group, (19") C_{1-6} alkyl-carbonyl group, (20") C_{1-4} alkyl-carbonyloxy group, (21") ω-oxo-ω-(tetrahydrobenzazepinyl) C_{1-6} alkyl group, (22") benzoyl group which may be substituted by 1 to 3 substituents selected from the group consisting of C_{1-4} alkyl, halogen, C_{1-4} alkoxy, mono- or di-C_{1-4} alkylamino, 5- to 7-membered cyclic amino group, nitro and hydroxy, (23") carbamoyl group, (24") mono or di C_{1-4} alkyl-carbamoyl group, (25") C_{1-6} alkylsulfonyl group, (26") oxo group and (27") heterocyclic group selected from pyridinyl, pyrazinyl, pyrimidinyl, quinolinyl, isoquinolinyl, naphthylidinyl, benzothiazolyl, benzoxazolyl, furanyl and thiophenyl; ring A is a benzene ring which may be further substituted by 1 to 3 substituents selected from the group consisting of a C_{1-4} alkyl, halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl-substituted amino, 5 to 7-membered cyclic amino, C_{1-4} alkyl-carbonylamino, C_{7-18} aralkyloxy, aminocarbonyloxy, mono-or di-C_{1-4} alkyl-substituted aminocarbonyloxy, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxy-carbonyl, carboxyl, C_{1-6} alkyl-carbonyl, C_{3-7} cycloalkyl-carbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsulfonyl, C_{3-7} cycloalkylsulfonyl and a phenyl, naphthyl, mono- or di-phenyl-C_{1-3} alkyl, phenoxy, benzoyl, phenoxycarbonyl, benzylcarbonyl, phenyl-C_{1-4} alkyl-carbamoyl, phenylcarbamoyl, phenyl-C_{1-4} alkyl-carbonylamino, benzoylamino, phenyl-C_{1-4} alkylsulfonyl, phenylsulfonyl, phenyl-C_{1-4} alkylsulfinyl, phenyl-C_{1-4} alkylsulfonylamino or phenylsulfonylamino which may be substituted by 1 to 4 substituents selected from the group consisting of a C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro, C_{1-6} alkyl-carbonyl and benzoyl.

3. A compound as claimed in claim 1, wherein R^1 is
   (i) hydrogen atom,
   (ii) a C_{1-4} alkyl group which may be substituted with a hydroxy group,
   (iii) a C_{2-4} alkynyl group,
   (iv) a phenyl-C_{1-3} alkyl group which may be substituted with one to three substituents selected from the group consisting of a halogen, nitro, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, hydroxy and phenylmethoxy group,
   (v) formyl group,
   (vi) a C_{1-4} alkyl-carbonyl group,
   (vii) benzoyl group,

(viii) a C_{1-4} alkoxy-carbonyl group,
(ix) pyridylcarbonyl group, or
(x) a mono- or di-C_{1-4} alkylcarbamoyl group.

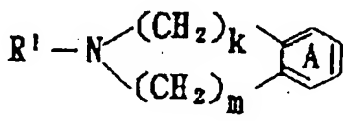
4. A compound as claimed in claim 1, wherein R^1 is (i) H, (ii) a straight-chain or branched C_{1-4} alkyl group, (iii) a phenyl-C_{1-3} alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of C_{1-4} alkyl, halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy and C_{7-18} aralkyloxy, (iv) a naphthyl-C_{1-3} alkyl group, (v) a C_{1-3} alkyl-carbonyl, (vi) a phenyloxycarbonyl or (vii) a C_{1-4} alkoxy-carbonyl.

5. A compound as claimed in claim 1, wherein R^1 is (i) H, (ii) a straight-chain or branched C_{1-4} alkyl group, (iii) a C_{1-4} alkyl-carbonyl group or (iv) a phenyl-C_{1-3} alkyl group which may be substituted by a C_{1-4} alkoxy.

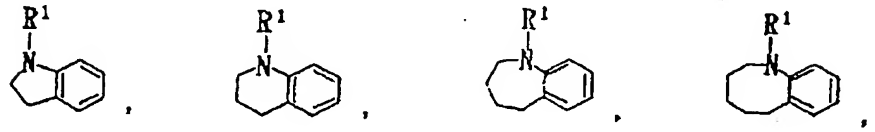
6. A compound as claimed in claim 1, wherein k + m is a whole number of 2 to 6.

7. A compound as claimed in claim 1, wherein k is a whole number of 0 to 2 and m is a whole number of 2 to 5.

8. A compound as claimed in claim 1, wherein the moiety in the formula [I] of



is



and R^1 is (i) H, (ii) a straight-chain or branched C_{1-4} alkyl group, (iii) a C_{1-3} alkyl-carbonyl group or (iv) a phenyl-C_{1-3} alkyl group which may be substituted by a C_{1-4} alkoxy.

9. A compound as claimed in claim 1, wherein the ring A is a benzene ring.

10. A compound as claimed in claim 1, wherein n is a whole number of 1 to 6.

11. A compound as claimed in claim 1, wherein R^2 is hydrogen atom or phenyl group.

12. A compound as claimed in claim 1, wherein R^2 is H.

13. A compound as claimed in claim 1, wherein R^3 and R^4 are independently
(i) a C_{1-4} alkyl group which may be substituted with a hydroxy group,
(ii) phenyl group or
(iii) a phenyl-C_{1-3} alkyl group which may be substituted with a halogen atom, or R^3 and R^4, taken together with the adjacent nitrogen atom, form
(i') a piperidinyl group which may be substituted with a phenyl-C_{1-3} alkyl group, a hydroxy group or oxo,
(ii') 4-oxo-1-phenyl-1,3,8-triazaspiro[4,5]decan-8-yl,
(iii') 1,2,3,4-tetrahydroisoquinolin-2-yl,

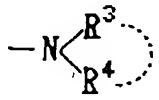
(iv') pyrrolidinyl,
(v') morpholinyl,
(vi') a homopiperazinyl group which may be substituted with a phenyl-C_{1-3} alkyl group, or
(vii') a piperazinyl group which may be substituted with (1) a phenyl-C_{1-3} alkyl group which may be substituted with a halogen atom, a C_{1-4} alkoxy group or a C_{1-4} alkylenedioxy group, (2) pyridyl group, (3) a benzoyl group which may be substituted with a halogen atom, (4) a C_{1-4} alkyl group which may be substituted with hydroxy group, 3-oxo-3[3-(phenylmethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]propyl, pyridyl, furyl or 2-methyl-thiazol-4-yl group, (5) formyl group, (6) a C_{1-6} alkyl-carbonyl group, (7) a phenyl group which may be substituted with a halogen atom, (8) hydroxyl group or (9) a diphenyl-C_{1-3} alkyl group.

14. A compound as claimed in claim 1, wherein one of R^3 and R^4 is H or a straight-chain or branched C_{1-4} alkyl group and the other is a straight-chain or branched C_{1-4} alkyl group, a phenyl-C_{1-3} alkyl group or a naphthyl-C_{1-3} alkyl group.

15. A compound as claimed in claim 1, wherein R^3 and R^4 taken together with the adjacent nitrogen atom, may form a pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or 1,2,3,4-tetrahydroquinolinyl group which may be substituted by 1 or 2 substituents selected from the group consisting of (1) formyl, (2) C_{1-4} alkyl-carbonyl, (3) hydroxy, (4) oxo, (5) pyridyl, (6) benzoyl which may be substituted by 1 to 3 halogen atoms, (7) straight-chain or branched C_{1-7} alkyl which may be substituted by 1 to 3 substituents selected from the group consisting of hydroxy, pyridyl, furyl, thiazol-4-yl and 2-methyl-thiazol-4-yl, (8) phenyl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, hydroxy and C_{1-4} alkylenedioxy, (9) C_{7-18} aralkyl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, hydroxy and C_{1-4} alkylenedioxy and (10) ω-oxo-ω-(tetrahydrobenzazepinyl) C_{1-6} alkyl.

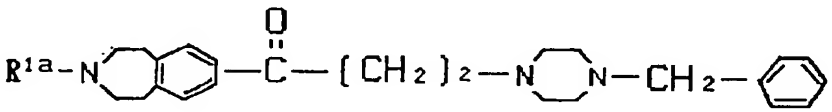
16. A compound as claimed in claim 1, wherein R^3 and R^4 taken together with the adjacent nitrogen atom, may form a 4-(phenylmethyl)-piperazin-1-yl or 4-[(2-methylthiazol-4-yl)methyl]-piperazin-1-yl.

17. A compound as claimed in claim 1, wherein n is a whole number of 3 to 8 when the group of the formula:



does not form a heterocyclic group and n is a whole number of 2 to 5 when the group forms a heterocyclic group.

18. A compound as claimed in claim 1, which is a compound of the formula:



wherein R^{1a} is
(i) a C_{1-4} alkyl group or
(ii) a phenyl-C_{1-3} alkyl group which may be substituted with a C_{1-4} alkoxy group.
or a pharmaceutically acceptable salt.

19. A compound as claimed in claim 1, which is 1-[3-[(4-methoxyphenyl)methyl]-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-3-[4-(phenylmethyl)piperazin-1-yl]-1-propanone or a pharmaceutically acceptable salt thereof.

20. A compound as claimed in claim 1, which is 1-[3-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-3-[4-(phenylmethyl)piperazin-1-yl]-1-propanone or a pharmaceutically acceptable salt thereof.

21. A compound as claimed in claim 1, which is 1-[3-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-3-[4-(phenylmethyl)piperazin-1-yl]-1-propanone or a pharmaceutically acceptable salt thereof.

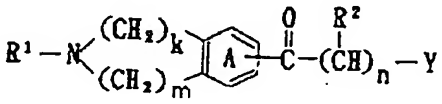
22. A compound as claimed in claim 1, which is 1-[3-(phenylmethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-3-[4-(phenylmethyl)piperazin-1-yl]-1-propanone or a pharmaceutically acceptable salt thereof.

23. A compound as claimed in claim 1, which is 1-[1-(phenylmethyl)-2,3-dihydro-1H-indol-5-yl]-3-[4-(phenylmethyl)piperazin-1-yl]-1-propanone or a pharmaceutically acceptable salt thereof.

24. A compound as claimed in claim 1, which is 1-[2-(phenylmethyl)-2,3,4,5-tetrahydro-1H-2-benzazepin-8-yl]-3-[4-(phenylmethyl)piperazin-1-yl]-1-propanone or a pharmaceutically acceptable salt thereof.

25. A compound as claimed in claim 1, which is 3-[4-[(2-methylthiazol-4-yl)methyl]piperazin-1-yl]-1-[3-(phenylmethly)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-propanone or a pharmaceutically acceptable salt thereof.

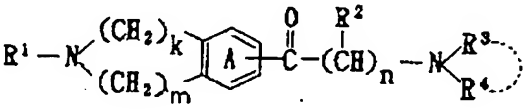
26. A compound of the formula:



[II]

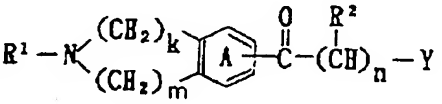
wherein Y is a leaving group; R^1, ring A, R^2, n, k and m are of the same meaning as defined in Claim 1 or a salt thereof.

27. A method for producing a compound of the formula:



[I]

wherein R^1 is H, an optionally substituted hydrocarbon group or an optionally substituted acyl group; ring A is an optionally further substituted benzene ring; n is a whole number of 1 to 10; R^2, R^3 and R^4 are independently H or an optionally substituted hydrocarbon group; R^3 and R^4 may form an optionally substituted heterocyclic group, taken together with the adjacent nitrogen atom; R^2's may be different from one another in the repetition of n; k is a whole number of 0 to 3; and m is a whole number of 1 to 8; provided that when k = 0 and m = 2, n is a whole number of not less than 2, or a pharmaceutically acceptable salt thereof, which comprises reacting a compound of the formula:



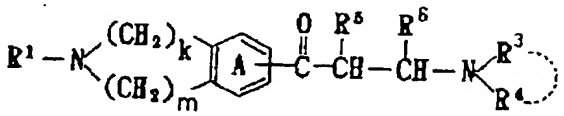
[II]

wherein Y is a leaving group; R^1, ring A, R^2, n, k and m are as defined above, or a salt thereof, with a compound of the formula:

(III)

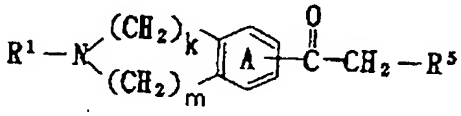
wherein R^3 and R^4 are as defined above, or a salt thereof.

28. A method for producing a compound of the formula:



(VI)

R^1 is H, an optionally substituted hydrocarbon group or an optionally substituted acyl group; ring A is an optionally further substituted benzene ring; R^3 and R^4 are independently H or an optionally substituted hydrocarbon group; R^3 and R^4 may form an optionally substituted heterocyclic group, taken together with the adjacent nitrogen atom; k is a whole number of 0 to 3; and m is a whole number of 1 to 8; provided that when k=0 and m=2, n is a whole number of not less than 2, R^5 is H or an optionally substituted hydrocarbon group, and R^6 is H or an optionally substituted hydrocarbon group or a Pharmaceutically acceptable salt thereof, which comprises reacting a compound of the formula:

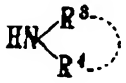


(IV)

wherein R^1, R^5, ring A, k and m are as defined above, or a salt thereof and a compound of the formula:

R^6-CHO [V]

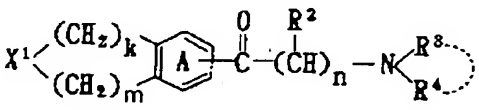
wherein R^6 is as defined above, with a compound of the formula:



(III)

wherein R^3 and R^4 are as defined above, or a salt thereof.

29. A cholinesterase inhibitor, which contains a compound of the formula:



(VII)

wherein X^1 is R^1-N (R^1 is H, an optionally substituted hydrocarbon group or an optionally substituted acyl group), O or S; ring A is an optionally further substituted benzene ring; n is a whole number of 1 to 10; R^2, R^3 and R^4 are independently H or an optionally substituted hydrocarbon group; R^3 and R^4 may form an optionally substituted heterocyclic group, taken together with the adjacent nitrogen atom; R^2's may be different from one another in the repetition of n; k is a whole number of 0 to 3; and m is a whole number of 1 to 8, or a pharmaceutically acceptable salt thereof.

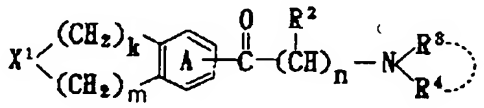
30. A pharmaceutical composition for a disease caused by acetylcholinesterase activity which contains an effective cholinesterase inhibiting amount of a compound of the formula [I] as claimed in claim 1 or a pharmaceutically acceptable salt thereof and a pharmacologically acceptable carrier.

31. A pharmaceutical composition for a disease caused by acetylcholinesterase activity which contains an effective cholinesterase inhibiting amount of a compound of the formula [VII] as claimed in claim 29 or a pharmaceutically acceptable salt thereof and a pharmacologically acceptable carrier.

32. A pharmaceutical composition as claimed in claim 30, in which the disease is senile dementia and/or Alzheimer's disease.

33. A pharmaceutical composition as claimed in claim 31, in which the disease is senile dementia and/or Alzheimer's disease.

34. A method of treating a disease caused by acetylcholinesterase activity which comprises administering a therapeutically effective amount of a compound of the formula:

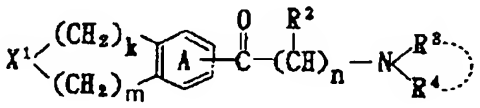


(VII)

wherein X^1 is R^1-N (R^1 is H, an optionally substituted hydrocarbon group or an optionally substituted acyl group), O or S; ring A is an optionally further substituted benzene ring; n is a whole number of 1 to 10; R^2, R^3 and R^4 are independently H or an optionally substituted hydrocarbon group; R^3 and R^4 may form an optionally substituted heterocyclic group, taken together with the adjacent nitrogen atom; R^2's may be different from one another in the repetition of n; k is a whole number of 0 to 3; and m is a whole number of 1 to 8, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier to a mammal suffering from such disease.

35. A method of treating a disease as claimed in claim 34, in which the disease is senile dementia and/or Alzheimer's disease.

36. Use of a compound of the formula:



(VII)

wherein X^1 is R^1-N (R^1 is H, an optionally substituted hydrocarbon group or an optionally substituted acyl group), O or S; ring A is an optionally further substituted benzene ring; n is a whole number of 1 to 10; R^2, R^3 and R^4 are independently H or an optionally substituted hydrocarbon group; R^3 and R^4 may form an optionally substituted heterocyclic group, taken together with the adjacent nitrogen atom; R^2's may be different from one another in the repetition of n; k is a whole number of 0 to 3; and m is a whole number of 1 to 8, or a pharmaceutically acceptable salt thereof as a component in the preparation of a cholinesterase inhibitor.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 93 10 3614

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 5)
P,Y	EP-A-0 487 071 (TAKEDA CHEMICAL INDUSTRIES, LTD.) 27 May 1992 * entire document * ---	1-25, 29-33,36	C07D401/06 A61K31/445 C07D209/08 C07D215/14 C07D223/16 C07D225/06 C07D403/06 C07D413/06
D,Y	EP-A-0 229 391 (EISAI CO., LTD.) 22 July 1987 * page 1, line 17 - page 2; claims 1,24,25 * ---	1-25, 29-33,36	
A	EP-A-0 326 106 (TAKEDA CHEMICAL INDUSTRIES, LTD.) 2 August 1989 * entire application * ---	1-25, 29-33,36	
A	EP-A-0 351 282 (SYNTHELABO) 17 January 1990 * entire application * ---	1-25, 29-33,36	
A	US-A-4 521 606 (AMERICAN HOME PRODUCTS CORP.) 4 June 1985 * entire application * --- -/--	1-25, 29-33,36	

TECHNICAL FIELDS SEARCHED (Int. Cl. 5)

A61K
C07D

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
MUNICH	29 JUNE 1993	HERZ C.P.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
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E : earlier patent document, but published on, or after the filing date
D : document cited in the application
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& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0403)

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 5)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	EP-A-0 294 647 (MERCK PATENTGESELLSCHAFT MBH) 14 December 1988 * compounds of formula II; examples * * claim 3 *	26	
X	EP-A-0 035 228 (OTSUKA PHARMACEUTICAL CO., LTD.) 9 September 1981 * reference example 22: 6-(4-chlorobutyryl)-3,4-dihydrocarbostyryl) *	26	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 5)

Incomplete search

Claims searched completely: 1-25, 27-33, 36
Claim searced incompletely: 26
Claims not searched: 34, 35 (Methods for treatment of the human or animal body; Article 52 (4) EPC)

Lack of conciseness

The defintion of the following substituent is too general and/or encompasses too broad a range of totally different chemical groups, only partly supported by examples given in the descriptive part of the application:

Y = leaving group (Claim 26)

The vast number of theoretically conceivable compounds resulting from the definition of this claimed substituent precludes a comprehensive search. Guided by the inventive concept as disclosed in the descriptive part of the present application the search has been limited to the examples

(c.f. Articles 83, 84 EPC, Rule 45 I.R., Guidelines Exam. Part B, Chapt. III, 3.6, 3.7).